Award Number: DAMD17-98-1-8611

TITLE: Natural History of Plexiform Neurofibromas in NF1

PRINCIPAL INVESTIGATOR: Bruce R. Korf, M.D., Ph.D.

CONTRACTING ORGANIZATION: Children's Hospital

Boston, Massachusetts 02115

REPORT DATE: October 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Machinery and Reducing Project (1704-0188) Washington DC 20503

Management and Budget, Paperwork Reduction Pro					
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DA			
	October 1999	Annual (01 Oct 98			
4. TITLE AND SUBTITLE Natural History of Plexiform Neur	rofibromas in NF1	-	. FUNDING N DAMD17-98-		
6. AUTHOR(S) Bruce Korf, Ph.D.					
7. PERFORMING ORGANIZATION NA Children's Hospital Boston, Massachusetts 02115 e-mail: bkorf@rics.bwh.harvard.edu	AME(S) AND ADDRESS(ES)	8.	8. PERFORMING ORGANIZATION REPORT NUMBER 10. SPONSORING / MONITORING AGENCY REPORT NUMBER		
9. SPONSORING / MONITORING AGUS. Army Medical Research and Fort Detrick, Maryland 21702-50	Materiel Command	5) 10			
11. SUPPLEMENTARY NOTES					
12a. DISTRIBUTION / AVAILABILITY Approved for public release; distribution unlimited	STATEMENT			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 Words) This report marks the completion of the first year of the project "Natural History of Plexiform Neurofibromas in NF1." The goals of the project are to test the utility of volumetric MRI in the measurement of plexiform neurofibromas, to use this approach to develop a body of normative data on the growth of plexiform neurofibromas, and to establish an infrastructure including radiology, statistical analysis, clinical database, tissue bank, and pathology review that will facilitate future clinical trials. This first year was devoted to developing the infrastructure of the project and initiating subject recruitment. Major accomplishments include holding a conference at the Banbury Center at which the protocol was refined, establishing MRI data transfer between the participating centers and the radiology analysis facility at WorldCare, creation of the clinical data entry forms, and establishing the communications between the participating centers and the coordinating center in Boston. Patient recruitment has begun, but has been delayed because of a longer than anticipated time required for the approval by the army IRB of the local informed consents. This process is nearing completion, and it is anticipated that subject recruitment will be complete within an additional six months.					
14. SUBJECT TERMS				15. NUMBER OF PAGES 168	
Neurofibromatosis				16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICA OF ABSTRACT Unclassifie		20. LIMITATION OF ABSTRACT Unlimited	

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89) Prescribed by ANSI Std. 239-18 298-102

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the

author and are not necessarily endorsed by the U.S. Army. Where copyrighted material is quoted, permission has been obtained to use such material. Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material. Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations. In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985). ✓_For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46. In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health. In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules. In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Table of Contents

Front Cover	Page 1
Standard Form (SF) 298, Report Documentation Page	
Foreword	Page 3
Table of Contents	Page 4
Introduction	Page 6
Progress Report for Statement of Work	Page 6
Task 1	Page 6
Task 2	Page 10
Task 3	Page 11
Task 4	Page 12
Key Research Accomplishments & Reportable Outcomes	Page 12
Conclusions	Page 12

Attachments

Α	Policy and Procedure Manual	Page 13
В	Army IRB Progress Report	Page 116
С	Neurofibroma Tumor Repository Progress Report	Page 119
D	Arie Perry, M.D., Pathologist	Page 121
E	Website	Page 125
F	WorldCare, Inc. Progress Report	Page 135
G	Workstation Invoice & Description	Page 141
Н	Study Tracking Worksheet	Page 144
I	Open House Announcement	Page 157
J	Consortium Meeting Agenda & Participants	Page 160

Introduction

This report marks the completion of the first year of the project "Natural History of Plexiform Neurofibromas in NF1." Plexiform neurofibromas are benign nerve sheath tumors that involve multiple nerve fascicles. They can lead to major disfigurement and morbidity. Treatment is currently limited to surgery, but complete resection is rarely possible. This project is intended to set the stage for clinical trials by developing a reliable approach to measuring tumor volume, as well as a body of normative data on growth rate of the tumors. It is also intended to assemble a consortium of clinical centers united by facilities in radiology, statistics, pathology, clinical data collection, and tissue banking.

The first year of the study was aimed at developing the infrastructure of the project and recruiting study subjects. The complexity of the project made it necessary to bring together all of the participants for a very productive three day meeting at the Banbury Center at Cold Spring Harbor, N.Y. in February. This made it possible to refine the entry and exclusion criteria, study protocol, and methods of communication and data tracking.

Although centers were technically prepared to recruit subjects by May, 1999, we encountered serious problems with Army IRB approval of each center's consent forms. In many cases this has required multiple iterations of revisions both by the Army and local IRB's, both creating frustration and delaying subject recruitment. Most of this process is now completed, and subject recruitment has begun. We expect recruitment to continue through the spring of 2000, likely necessitating extension of the study, which will be possible given that delays in recruitment reduced expenditures this year.

The following report will focus on our progress in setting up the study infrastructure and will exemplify some of the radiological data received to date.

Progress Report for Statement of Work by Task

Task 1. Complete development of study infrastructure – Months 1-6

a. IRB approval at all clinical sites

All of the clinical sites have obtained IRB approval from their own institutions. As of October 1, 1999 only 4 clinical centers have obtained IRB approval from the US Army. This is mainly due to the unanticipated lengthy turn-around time for Army IRB approval, and staff turnover at the MCMR last winter. Copies of the Children's Hospital consent forms, which have been approved by both Children's Hospital IRB and the Army IRB, are located in Appendix B of Attachment A. A complete listing of

the status of Army IRB approval of participating clinical centers provided by the Army is located in Attachment B.

A complete list of all participating centers is located Appendix A of the Policy and Procedure Manual (Attachment A). We have also added two centers to the consortium since the approval of this grant. The following Principal Investigators and their centers have been added:

Jan Friedman, M.D., Ph.D. University of British Columbia British Columbia Children's Hospital Vancouver, BC CANADA

Fernando Kok, M.D. Universidad de Sao Paulo San Paulo, BRAZIL

In the original application we stated that John Mulvihill, M.D., Ph.D. would be the Principal Investigator at the University of Pittsburgh. Dr. Mulvihill has since taken a new position at the University of Oklahoma, Children's Hospital of Oklahoma. Dr. Mulvihill is continuing his role in the consortium at the University of Oklahoma.

b. Complete clinical data entry forms and test electronic transfer of clinical data

We elected not to use electronic clinical data entry forms to collect the data. This decision was based on concerns about confidentiality of data and the development of scannable forms by The International Neurofibromatosis Database at the University of British Columbia. This simplified data entry, avoided concerns about transmittal of clinical data over the internet, and permitted the participating centers to maintain a paper copy of clinical data that is necessary for a clinical trial. A data entry form specific to this study of plexiform neurofibromas was created. We are also using the standard demographic data collection form as well as the core NF data collection form. By using these forms, patients from this study will be entered into the database in the same format as patients from centers that regularly participate in the International Neurofibromatosis Database. Data collection forms and instructions for their use are located in Appendices G-H of the Policy and Procedure Manual (Attachment A).

c. Organize package of materials for pathology review and tissue repository

Please see Section I of the Policy and Procedure Manual located (Attachment A). In this manual we have included instructions for collection of blood and serum.

David Gutmann, M.D., Ph.D. has submitted a progress report for the Neurofibroma Tumor Repository. Please see Attachment C.

It has been necessary to change the structure of the pathology review core. This was originally a subcontract to Dr. David Wolfe at Mt. Sinai School of Medicine. We have found it to be awkward, however, to split the responsibility of tissue collection between two sites, namely the tissue bank and the pathology review site. Moreover, other commitments by Dr. Wolfe have made it difficult for him to provide the level of attention to this project that it requires. We therefore propose that the pathology review facility be moved to Washington University School of Medicine in St. Louis, the site of the tissue bank. Dr. Arie Perry, a neuropathologist at Washington University, has agreed to take responsibility for this role. His CV and a letter of agreement are presented in Attachment D. No funds have been expended for neuropathology review to date, given the problems in the Mt. Sinai facility and the fact that delays in IRB approval have delayed the accession of study subjects. As subject recruitment is now accelerating, this is a good time to make the change to consolidate all tissue collection functions of the project into a single facility.

d. Set up listserve and website

The website has been constructed, and will be available to the public by the end of November. A printout of the website is located in Attachment E.

We are in the process of creating a listserve. Communications between participating centers have been accomplished by email and fax, reducing the urgency of a listserve for communication.

e. Test MRI data transfer

WorldCare, Inc. has submitted a progress report, which is presented in Attachment F.

f. Purchase workstation and prepare data entry forms at WorldCare.

The workstation was purchased in November of 1998. Please see the invoice and description of the equipment in Attachment G.

Data collection forms have been created to track MRI data, which is sent over the Internet using the FTP method, or saved to an optical disk and shipped. There is a data collection form, which must be completed to document the MRI, and three acquisition protocols. The acquisition protocol used depends on the location of the plexiform neurofibroma. Copies of these forms are located in Appendices L-N of the Policy and Procedure Manual (Attachment A).

When a file is transferred or shipped, the clinical center faxes the data collection form and the acquisition protocol to Mary Sanford, the research study coordinator, at Children's Hospital. This alerts the study coordinator that an MRI has occurred and the step is checked off on the project monitoring flowsheet. Once WorldCare has received the data, and confirmed that it is readable, a Confirmation Fax is sent to both Children's Hospital and the center from which it originated. A flowchart of the process in located in Appendix O of the Policy and Procedure Manual (Attachment A).

g. Prepare project monitoring flowsheet at Children's Hospital

At this time we are using an Excel spreadsheet to track progress. The workbook is designed to track the data for the entire duration on the study, which will include 7 visits per study subject. This report only includes patient visit #1 of the study-tracking workbook (Attachment H), because no patients have been seen more than once. There are 6 worksheets (Groups A-F) for the 3 plexiform categories and for both children and adults.

h. Prepare recruitment letters for study subjects

We decided to hold an open house rather than sending out a patient recruitment letter. In addition to the open house, Gretchen Schneider, M.S., reviewed medical records of NF patients with plexiform neurofibromas and personally contacted them about possible enrollment in the study.

i. Publicize study to NF community

Children's Hospital held an open house to inform the public of the progress of NF research and to publicize the study on July 16, 1999. Bruce Korf, and Gretchen Schneider presented an overview of the study for NF patients and families, as well as information on upcoming clinical trials. A copy of the announcement, which was mailed to over 500 NF patients, is located in Attachment I.

Task 2. Recruitment of Study Subjects – Months 6-12

- a. Centers contact prospective study subjects
- b. Enrollment of study subjects
- c. First MRI and clinical data received

Tasks a-c have been delayed due to the problems with the IRB approval process. Once centers receive Army IRB approval they immediately begin enrollment. All centers have been actively promoting and recruiting patients.

Please see the Study-Tracking Sheet (Attachment H) for enrollment and clinical data received.

Please see the progress report provided by WorldCare for information on MRI data received (Attachment F).

d. Review of clinical entry criteria

A three-day meeting devoted to this study was held in February 1999 at the Banbury Center in Cold Spring Harbor, N.Y. This meeting was jointly sponsored by the U.S. Army through this project and by the National Neurofibromatosis Foundation. A complete list of participants and the meeting agenda are provided in Attachment J. All of the core facilities of the project and all of the participating centers except one (Australia) were

represented at the meeting. The meeting was intended to review the protocol and make amendments prior to the initiation of subject recruitment. Following the meeting, a detailed protocol manual (Attachment A) was created and provided to all the participating centers. Details of these changes are located in Section D of Attachment A. Changes were made from the original protocol as follows:

- 1. The three study groups were modified. Originally these were cranial nerve, spinal nerve, and peripheral nerve. It was decided that there might be ambiguity in determining the nerve of origin of some tumors, and that a more clinically based classification scheme would be easier to use in a consistent manner. Therefore, the three study groups were changed to head/neck, trunk/extremity externally visible, and trunk/extremity not externally visible. The definition of plexiform neurofibroma also was clarified, to confine the study to tumors with a potential to cause disfigurement or functional disability.
- 2. Exclusion criteria were clarified to include previous radiation therapy, current antineoplastic therapy, surgery within six months of the onset of the study (excluding biopsy), and failure to obtain an MRI within 60 days of enrollment.
- 3. Changes were made in the MRI acquisition protocol to insure complete coverage of the neurofibroma and minimize scanning time.

e. Test of inter-observer reproducibility of designation of tumor margins by MRI

Due to the delayed patient recruitment we have been unable to complete the Reproducibility Study as planned. A meeting of the steering committee occurred on September 10, 1999 to design the Reproducibility Study. The radiologists working on the study from Children's Hospital are meeting at WorldCare November 2, 1999 to review the first sets of data. A final report is expected by the end of November.

Task 3. Data Acquisition and analysis – Months 13-42

Not Applicable at this time

Task 4. Interpretation of Data – Months 43-48

Not Applicable at this time

KEY RESEARCH ACCOMPLISHMENTS

- International meeting at Banbury Center of all study participants to refine and finalize the protocol in February 1999
- Completion of procedures and policies manual
- Set up of MRI data analysis center at WorldCare and successful transfer of test data from participating clinical centers
- Establishment of communication system between clinical centers and coordinating center and record keeping system to track data acquisition
- Establishment of collaboration with Pediatric Brain Tumor Consortium to conduct clinical trials of farnesyl transferase inhibitor and angiogenesis inhibitor for plexiform neurofibromas

It should be noted here that there has been one significant unanticipated challenge, involving army IRB approval of the informed consents used by all participating centers. Army review of the consent forms occurred very slowly in the winter and early spring of 1999, largely due to staff turnover at the MCMR; indeed for a significant period of time we were not able to receive updates on the progress of IRB approval at all. The process has subsequently moved very slowly, often with forms going back and forth over a period of many months between the army IRB and local IRB's. In some cases, centers were informed that they would be approved by one staff member, only to be told that they were not approved weeks later by a different staff member. We have found that, once approval is granted, subject recruitment goes quickly and smoothly (recruitment at Children's Hospital was completed within about 6 weeks). The process of IRB approval is nearing completion, but this delay will require us to extend the study period by 6-12 months. There should be sufficient unexpended funds related to cover the costs of this extension, due to the reduced level of clinical activity during this first year.

CONCLUSIONS

The infrastructure for the study is now completed, and data transfer has been tested. The first MRI data has been received at WorldCare, and the study of reproducibility of volumetric analysis is now underway. Although subject recruitment has been delayed because of difficulties with IRB approval, this obstacle is mostly resolved, and we are confident that subject recruitment will be completed over the next 6 months.

Attachment A

NATURAL HISTORY OF PLEXIFORM NEUROFIBROMAS IN NF1

PROCEDURES AND POLICIES MANUAL

Version 3.00

May 13, 1999

Section A

Table of Contents

Table of Contents Section A

Introduction Section B

Overview and Goals of Project Organizational Structure

Administration Section C

Principle Investigator Executive Committee Publication Policy

Subject Recruitment Section D

Entry Criteria
Informed Consent

US Army Volunteer Registry Database

Registration Withdrawal from Study Subject Reimbursement

Adverse Events

Patient Visit Protocol Section E

Clinical Assessment Protocol Section F

Timing

Clinical Evaluation and Data Entry

Measurements Photography

MRI Protocol Section G

Timing of MRI Arrangements for MRI Payment for MRI

MRI Data Collection and Transmittal Protocol Section H

WorldCare, Inc.

MRI Data Collection Procedure

File Transfer Protocol (FTP) Procedure (Preferred Method of Data Transfer)
Data Archival and Optical Disk Shipment Procedures (Alternative Method)

Plexiform Neurofibroma Tumor Repository Section I

Introduction

Instructions for Sample Collection

Shipping Instructions

Pathology Review Section J

PENDING

Appendices

Participating Centers	Appendix A
Informed Consent	Appendix B
US Army Volunteer Registry	Appendix C
Patient Registration Forms	Appendix D
Patient Withdrawal Forms	Appendix E
Adverse Events Forms	Appendix F
International Database	Appendix G
Sample Scannable Clinical Data Collection Forms	Appendix H
Tanner Stages	Appendix I
MRI Reimbursement Forms	Appendix J
WorldCare, Inc. Site Survey	Appendix K
Data Collection Forms (MRI)	Appendix L
Acquistion Protocols (MRI)	Appendix M
Data Collection Confirmation Fax (MRI)	Appendix N
Work Flow Diagram	Appendix O
Pre-Dated Invoices	Appendix P

Section B

Introduction

This manual provides a description of procedures and policies for participants in the project "Natural History of Plexiform Neurofibromas in NF1" supported by the U.S. Army. The contents are subject to approval and revision by the executive committee of the project. Questions or comments should be directed to:

Principal Investigator:

Bruce R. Korf, M.D., Ph.D. Division of Genetics Children's Hospital 300 Longwood Ave. Boston, MA 02115

Phone: 617-355-6091 Fax: 617-355-7588

e-mail: korf@hub.tch.harvard.edu

project home page:

Study Coordinator:

Mary Sanford Division of Genetics Children's Hospital 300 Longwood Ave. Boston, MA 02115 Phone: 617-355-3479

Fax: 617-355-7588

e-mail: sanford_m@hub.tch.harvard.edu

Medical Coordinator:

Gretchen Schneider, M.S. Division of Genetics Children's Hospital 300 Longwood Ave. Boston, MA 02115

Phone: 617-355-4699 Fax: 617-277-5933

e-mail: schneider_g@hub.tch.harvard.edu

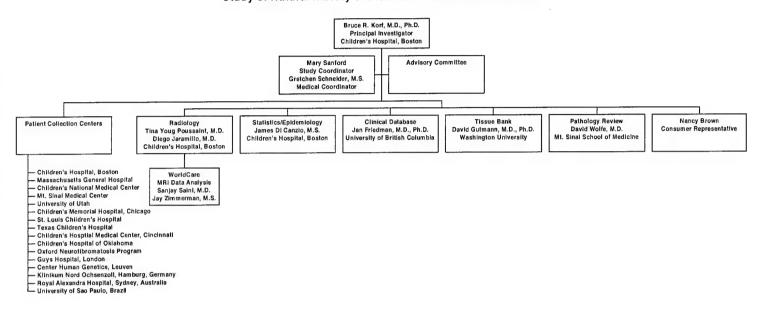
Overview and Goals of Project

This is a four-year study, the overall objective of which is to set up a system that will facilitate clinical trials of potential therapies for plexiform neurofibromas in NF1. These tumors are unpredictable in terms of rate of growth and are difficult to measure. We will set up a network of clinical centers and will follow the growth of plexiform neurofibromas using volumetric MRI. These centers will be supported by a tissue bank, in which tissue samples will be made available to investigators throughout the world. In addition there will be a database used to track clinical information about patients with NF1 and a standard pathology review for any biopsy material. The first stage of this project will involve setting up the infrastructure. Subject recruitment will begin in April 1999. The study will then continue over a three-year period, during which patients will be present for clinical assessments and MRIs. The protocol includes an algorithm for determination of the time for repeat MRI's; clinical assessments will occur at 6 monthly intervals. The last six months of the study will be devoted to data analysis.

Study Objectives

- **A.** Determine the efficacy of volumetric MRI for measurement of the growth rate of plexiform neurofibromas.
- **B.** Provide a body of normative data on the growth rate of plexiform neurofibromas. Although limited by a relatively short study period, the following hypotheses will be tested:
 - i) Most plexiform neurofibromas grow out of proportion with somatic growth for a period of time during childhood but reach a plateau by the end of puberty;
 - ii) Patterns of neurofibroma growth may vary from patient to patient but there are no systematic differences in growth patterns according to location of the neurofibroma in the body;
- C. Establish a consortium of clinical centers supported by a tissue repository and central review of pathology, radiology, and statistical data.

Study of Natural History of Plexiform Neurofibromas in NF1



Section C

Principal Investigator

Bruce R. Korf, M.D., Ph.D. Children's Hospital and Harvard Medical School, Boston

Executive Committee

Bruce R. Korf, M.D., Ph.D.
Gretchen Schneider, M.S.
Mary Sanford
Tina Young Poussaint, M.D.
Diego Jaramillo, M.D.
Jim DiCanzio, M.S., Ph.D.
Jay Zimmerman, M.S.
David Gutmann, M.D., Ph.D.
David Wolfe, M.D., Ph.D.,
Jan Friedman, M.D., Ph.D.
Nancy Brown

Participating Centers

Please see Appendix A

Publication Policy

A report of the study of MRI volumetric data will be prepared by the principal investigator, radiologists, and statistician, with the members of the consortium listed as co-authors. Other papers may be prepared by any member of the consortium using data from their own patients, or data from patients at other centers with the permission of the relevant investigators.

Section D

Entry Criteria

- A. Diagnosis of Neurofibromatosis: All study subjects will fulfill diagnostic criteria for NF1.
 - i) Six or more café-au-lait macules
 - a. 1.5cm or larger in postpubertal individuals
 - b. 0.5 cm or larger in prepubertal individuals
 - ii) Two or more neurofibromas of any type *or* 1 or more plexiform neurofibroma
 - iii) Freckling in the axilla or groin
 - iv) Optic glioma (tumor of the optic pathway)
 - v) Two or more Lisch nodules (benign iris hamartomas)
 - vi) A distinctive bony lesion
 - a. Dysplasia of the sphenoid bone
 - b. Dysplasia or thinning of long bone cortex
 - vii) A first degree relative with NF-1
- **B. Plexiform Neurofibroma:** A plexiform neurofibroma fulfilling entry criteria for the study will be defined as a diffuse soft tissue or nerve enlargement in a patient with NF1 that is causing or has potential to cause disfigurement or functional disability.
- C. Distribution of Plexiform Neurofibromas by site: A total of 300 plexiform neurofibromas will be studied, consisting of 100 tumors in the following three groups (based on region of maximal involvement):
 - 1. Head and Neck
 - 2. Trunk and Limbs (externally visible)
 - 3. Trunk and Limbs (internal) [spinal plexiform neurofibromas involve two or more levels with connection between the levels or extending laterally along the nerve]

D. Subject Ascertainment: Study subjects will be ascertained at any of the participating clinical centers. It is expected that these will include subjects already followed in these clinics, as well as newly diagnosed patients.

E. Exclusion Criteria: Exclusion criteria will be:

- i) Presence of metallic implant that will make the patient unable to have MRI studies
- ii) Presence of medical or psychological condition that will make the patient unable to tolerate MRI studies or anesthesia (if needed)
- iii) Inability to image tumor or define tumor margins by MRI (which may be determined after the initial study)
- iv) Failure to obtain initial MRI within 60 days of enrollment
- v) Previous radiation therapy to site of plexiform neurofibroma
- vi) Surgery involving the plexiform neurofibroma (excluding biopsy) within a six month period before enrollment
- vii) Current antineoplastic therapy

Informed Consent

The protocol has been approved by the U.S. Army IRB and the Children's Hospital, Boston IRB. Each PCC is responsible for obtaining approval from its respective IRB. The informed consents from Children's Hospital are in Appendix B. It is expected that similar forms will be used at each PCC, with only minor institution-specific changes.

US Army Volunteer Registry Database

The information is used to respond to Freedom Information Act requests for information by a subject of his or her participation in research sponsored by our Command. We also maintain the VRDB to ensure that we can, if necessary, provide new information to individual subjects regarding their participation in a DOD sponsored study. Access to the information maintained in the VRDB is restricted and is protected by the Privacy Act of 1974. The Privacy Act provides for criminal penalties for unauthorized use or release of information.

Every participant must fill out the Volunteer Registry Data Sheet (Appendix C). The form is to be mailed directly to the US Army. Do NOT send the form to Children's Hospital.

Registration

Subjects will be registered in the study when the clinical coordinator from a PCC calls the study coordinator at Children's Hospital, Boston and provides a completed Subject Registration Form (Appendix D). The Medical Coordinator and the Principal Investigator will review the subject information. Subjects will be admitted to the study if entry criteria are fulfilled, no exclusion criteria are met, and there is an appropriate opening in the study in one of the six groups based on subject age and location of the plexiform neurofibroma. It is not permissible for a single subject to be entered into more than one study group, if more than one plexiform neurofibroma is present. It is also not permissible for multiple members of the same family to be entered into the study.

Withdrawal from Study

Subjects may withdraw voluntarily from the study at any time, or may be dropped from the study due to non-participation. Non-participation will be defined as being more than 3 months late for a scheduled clinical or radiological follow-up. Subjects who have surgery on the plexiform neurofibroma other than biopsy or antineoplastic therapy will be excluded from data analysis, but may continue to have volumetric analysis of MRI data at the discretion of the steering committee, with the data segregated from other subjects. A Subject Withdrawal Form (Appendix E) should be provided to the Principal Investigator.

Subject Reimbursement

There is no provision to reimburse subjects for participation in the study.

Adverse Events

Adverse events related to the study must be reported within 72 hours to the Principal Investigator using the Adverse Events Report Form (Appendix F).

Section E

A. Timing

Patient visits will occur every 6 months, some including **only** a clinical assessment, others including **both** a clinical assessment and a MRI.

B. Clinical Assessments

Procedures for collection and transmission of clinical data are located in Section F.

C. MRIs

Procedures for collection and transmission of MRI data are located in Sections G $\&~\mathrm{H}.$

Section F

Clinical Assessment Protocol

Timing

Each study subject will receive a complete physical examination at the start of the study, and at intervals of every 6 months during the three year study period. Subjects will be seen whether or not an MRI is scheduled.

Clinical Evaluation and Data Entry

Clinical evaluations will be performed by the physician associated with each PCC. Standard physical examination will be done, and the clinical data entry form will be filled in (Appendix H). Instructions for using the International Database are located in Appendix G. A copy of the clinical data form will then be sent to Children's Hospital, Boston, which will then forward the form to University of British Columbia for entry into the computer database.

Measurements

Plexiform neurofibromas visible on the surface will be measured both with a tape measure and/or with calipers. At least two measurements, representing largest diameters along two perpendicular lines, will be taken. Multiple measurements will be done for irregularly shaped tumors, as necessary. Landmarks will be recorded by the clinician to ensure that measurements are made in a consistent manner from visit to visit.

Photography

Plexiform neurofibromas that are visible on the body surface will be photographed every six months at the time of clinical evaluation. Photography will be done using a 35 mm camera using Ektachrome 100 film or equivalent. A size marker will be taped to the skin in the field of view, and the neurofibroma will be photographed so that it fills the frame. Frontal and side images will be taken, as appropriate. Copies of photographs will be sent to the study coordinator, identified by the subject ID number.

Section G

Timing of MRI

All subjects will have an MRI done at the time of recruitment into the study, at one year, and at three years. Additional scans may be done at the discretion of the physician for clinical indications.

Arrangements for MRI

MRI scans will be scheduled by the PCC clinical coordinator using the MRI scanner at the PCC. The clinical coordinator will notify Mary Sanford at Children's Hospital, Boston of the anticipated date of the MRI and will notify the radiology technologist of the study protocol.

Payment for MRI

The costs of MRI will be billed to patient's insurance. Limited funds are available to cover the cost of MRI's for patients who do not have insurance, or for those in whom insurance coverage is denied. Reimbursement for MRI will only be done at a research rate and will require prior approval by the Principal Investigator. The form to request reimbursement for MRI by the study is in Appendix J.

MRI Acquisition Protocol

See Appendix M

Please Note: The MRI acquisition protocols are separated into Head/Neck, Trunk and Extremities, and Spine. These differ from the three classes of subjects recruited into the study. The MRI protocol to be used depends on the anatomical location of the plexiform neurofibroma, and should be reviewed by the clinician and radiologist doing the study.

WorldCare, Inc.

Introduction:

WorldCare, Inc. has developed these Standard Operating Procedure (SOP) Guidelines in support of the Neurofibromatosis 1 Study. This manual supports the operations and data tracking of the **Patient Collection Centers**. This support is required until the conclusion of the Neurofibromatosis 1 Study, as determined by The United States Army Research and Material Command.

<u>Prior</u> to the collection of any study data, each Patient Collection Center should complete the WorldCare Site Survey in Appendix K. A completed copy of this survey must be forwarded to WorldCare before any actual study data can be accepted.

Proprietary Statement:

This guideline is an internal document provided by WorldCare, Inc. All material pertaining to **Data Collection Procedure**, File Transfer Protocol Procedure, and Data Archival and Optical Disk Shipment Procedure and WorldCare procedures is confidential and proprietary. Do not distribute or duplicate.

Disclaimer:

This procedure manual is furnished under a license and may be used and copied only in accordance with the terms of such license and with the inclusion of the above copyright notice. This manual or any other copies thereof may not be provided or otherwise made available to any other person. No title to and ownership of the software is hereby transferred.



MRI Data Collection Procedure

Responsibility:

PCC Technician, PCC Clinical Coordinator

Requirements:

Data Collection Form (Appendix L), Acquisition Protocol

(Appendix M)

Definition The Data Collection Procedure (DCP) outlines the steps used to capture patient and visit information and MRI data. In this procedure, the Patient Collection Center (PCC) technician acquires information that will be transferred to either Children's Hospital by optical disk or to the WorldCare Measurement Center (WC-MC) by FTP. The PCC technician should perform the series indicated by the NF1 Acquisition Protocol in addition to the normal clinical scan if it is not already included.

Note: The standard phantom calibration will be performed each morning prior to any data acquisition to ensure scanner is functioning within normal operating parameters.

Start Procedure

Baseline visits:

- 1. Patient ID #s will be assigned by the NF1 Research Coordinator, Mary Sanford, at Children's Hospital when patients are registered. This ID # must be used for all follow-up scans. After an ID number has been assigned, the PCC Clinical Coordinator will contact CH with the date that the patient will be scanned.
- 2. Gather materials identified in this procedure's requirements listed above. Record all relevant information on the Data Collection Form in the appropriate spaces.
- 3. Follow the NF1 Acquisition Protocol used to perform each scan. If there are any changes to the NF1 Acquisition Protocol, please record the change and the reason for the change in the space provided.

The PCC Technician must sign both the NF1 Acquisition Protocol and the DCF before it is sent to Children's Hospital. The PCC Clinical Coordinator must also sign the acquisition protocol.

4. Send the signed originals of the NF1 Acquisition Protocol and Data Collection Form (DCF) to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital.

Follow-up visits:

- 1. Gather materials identified in this procedure's requirements listed above. Record all relevant information on the Data Collection Form in the appropriate spaces.
- 2. Follow the NF1 Acquisition Protocol used to perform each scan. If there are any changes to the NF1 Acquisition Protocol, please record the change and the reason for the change in the space provided.

The PCC Technician must sign both the NF1 Acquisition Protocol and the DCF before it is sent to Children's Hospital. The PCC Clinical Coordinator must also sign the acquisition protocol.

3. Send the signed originals of the NF1 Acquisition Protocol and Data Collection Form (DCF) to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital.

If the scanner software or hardware is upgraded during the course of the study for the follow up visits, the PCC technician is encouraged to perform additional scans to test the variability between the old and new scanners. Additional scans with improved quality will benefit the data extracted.

File Transfer Protocol (FTP) Procedure (Preferred Method of Data Transfer)

Responsibility: PCC Technician, PCC Clinical Coordinator

Requirements: Data Collection Form, Signed Acquisition Protocol

Definition The File Transfer Protocol procedure completes the patient collection process by transferring images to WCMC and notifying CH that patient images have been acquired and are being shipped. Copies of the Data Collection Form and signed Acquisition Protocol are sent to CH. This procedure also records data tracking and the activities associated with the movement of information between the PCC and CH.

Start Procedure

- 1. Gather materials identified in this procedure's requirements.
- 2. Make a copy of the Data Collection Form and the signed Acquisition Protocol and file them in patient file. The *original* DCF form and signed Acquisition Protocol should be sent to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital.
- 3. To transfer data:
 - a) Start FTP Client (WS_FTP95 LE on Windows NT/95, XFTP on Unix or Fetch on Macintosh)
 - b) Log into host252.ct.worldcare.com
 - ♦ For Host name/address, enter host252.ct.worldcare.com
 - ♦ For Host type, enter "automatic detect"
 - ♦ For User ID, enter NF1
 - ♦ For password, enter NF1
 - c) Select "binary" mode
 - d) Navigate to NF1 directory
 - e) Create a directory PATID_VISIT# to transfer
 - f) Select files under local system and transfer to remote system by selecting the appropriate arrow button

Data Archival and Optical Disk Shipment Procedures (Alternative Method)

Responsibility:

:

PCC Technician, PCC Clinical Coordinator

Requirements:

Optical Disk, Data Collection Form, Signed Acquisition Protocol

Note: WorldCare's preferred data transfer method for the Neurofibromatosis 1 study is FTP. If the site(s) have the capacity (i.e. passage through a firewall, internet connectivity) to transfer data electronically to WC, the FTP procedure should be used.

Definition The Data Archival and Optical Disk Shipment Procedure archives the acquired patient images onto optical disk and forwards the optical disk package to CH. This procedure will produce an original hard copy output for each set of patient images on optical disk. This output is packaged and sent to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital. A copy of the Data Collection Form and the signed NF1 Acquisition Protocol are forwarded to CH along with the optical disk. This procedure also records data tracking and the activities associated with the movement of information between the PCC and CH.

The optical disk used for this procedure is a WORM disk provided to the Clinical Coordinator by the WC-MC. However, the disk will only be provided if the PCC is unable to perform the FTP procedure. For further description of WORM, see explanation below.

Start Procedure

- 1. Gather materials identified in this procedure's requirements. All relevant patient information should be recorded on the optical disk label for archiving purposes.
- 2. Produce an original hard copy output of the data set.
- 3. Each WORM disk will have two labels. One label at the top of the disk and a different label for the side of the disk.
 - a) The top of the disk (the label visible when the optical disk is in its cover) will already be labeled by the WC-MC technician in the following manner:

The PCC Clinical Coordinator should confirm that the disk is labeled properly.

Example:

NF1 = Study Abbreviation

MGH = Facility initials (see Associated Acronyms)

A or B = Side of disk which contains data

= Disk Number (1=first, 2=second, 3...)

Final Label:

NF1-MGH-A-D2

b) The PCC Clinical Coordinator must fill in the side label for each patient visit stored on the disk. The side label of the optical disk (the label on each side of the disk) should indicate which patients are included on each disk and the patient visit number.

Example:

123-4321-567 =

Patient ID number

V1/25/99

Visit Date

Side Label:

123-4321-567-V1/25/99

The PCC Clinical Coordinator should confirm that the disk is labeled properly.

- 4. Complete the Data Collection Form with the required patient information and shipping information. Include the DHL shipping number and the date the optical will be shipped.
- 5. Place one copy of the Data Collection Form in the Patient Study File stored at the PCC.
- 6. Place one copy of the signed Acquisition Protocol in the Patient Study File stored at the PCC.
- 7. Ship the optical disk along with the originals of the Data Collection Form and the signed Acquisition Protocol to the NF1 Research Coordinator, Mary Sanford, at Children's Hospital. The copies of the DCF form and the signed NF1 Acquisition Protocol should be filed at the PCC in the Patient Study File.

The PCC Clinical Coordinator must review all documentation before filing at the PCC and sending to CH. The PCC Clinical Coordinator is also responsible for tracking all packages shipped and received for the purposes of the NF1 Study.

WORM Optical Disk Explanation

For each patient visit, the assigned Clinical Coordinator at each PCC will provide the optical disks at the time of each scan. The type of optical disk used for the transfer and archival of patient data is a WORM (Write Once Read Many) optical disk. The patient data on this disk can not be written over. However, the disk may be used for other patient visits if there is additional space left on the optical disk following each visit (approximately 4-5 visits per disk). Therefore each site will be provided with an optical disk that may be shipped to Children's Hospital following a patient visit and then returned to the site once the data has been entered in to the database at WorldCare. These disks will act as carriers of patient data for the NF1 study and each disk will be used until it runs out of space. When the WC-MC receives a full optical from the PCC, the WC-MC will ship a new empty disk to the Clinical Coordinator, at the PCC.

Section I

Plexiform Neurofibroma Tumor Repository

Introduction

The Washington University Tumor Repository Core will process whole blood from aliquots of peripheral leukocyte cell pellets. Tissue and white cell pellets will be stored along with basic patient identifiers and data in the Repository Core Facility. The Washington University Department of Neurology will be billed for procurement services on a per specimen basis. The Repository will also bill for a yearly specimen storage fee.

Genomic DNA, RNA, cDNA, protein lysates, and histological sections from collected material will be made available to investigators after appropriate panel review. There will be a nominal specimen processing charged billed to each requesting investigator for samples distributed.

Instructions for Sample Collection

1. Three to five days prior to tumor resection, please call or fax Ms. Louise Burrell at the Washington University Cancer Center Tumor Repository. Provide the name and shipping address of the physician (probably a pathologist) responsible for tissue acquisition.

Phone: 314-454-7919 Fax: 314-454-5525 24 hr Pager: 314-424-9106

- 2. A shipping module will be mailed via overnight express to the physician indicated.
- 3. At the time of resection, tissue should be IMMEDIATELY transported from the operating room to the attending surgical pathologist. Material not needed for clinical management should be cut into pieces less than 1 cm³ in size, placed in the appropriately labeled specimen bag, and IMMEDIATELY snap frozen in liquid nitrogen or -50 degree histology cryobath. Once frozen, the tissue may be maintained in the cryobath or a -70 degree freezer until it is ready for shipment. It is very important that: (1) Tissue be frozen as soon as possible after resection; (2) Tissue be frozen rapidly; and (3) Tissue be maintained at or below -50 degrees until shipment.
- 4. If possible, please collect 20 cc of blood from each patient in purple top (NaEDTA) tubes. From each parent, please collect 20 cc of blood in purple top (NaEDTA) tubes. Label all tubes with patient's name and/or parent's relationship to patient. Store blood at 4 degrees until shipping. **DO NOT FREEZE THE BLOOD**.

Shipping Instructions

Shipping modules will be mailed via overnight express to the physician indicated by Louise Burrell.

Please call Ms. Louise Burrell at The Washington University Cancer Center at (314) 454-7919 prior to shipping.

<u>Do not send specimens on Friday or the day preceding a holiday.</u> Store samples until Monday at the appropriate temperature.

Blood

- 1. Samples should be sent at room temperature. They need to be carefully wrapped to protect them from breakage. All shipments are sent priority one.
- 2. Label all tubes of blood with NF Patient ID # and/or relation to patient.

Tissue Sample

- 1. Label all sample packaging with NF Patient ID #.
- 2. Add ~8 lbs. of dry ice to shipping container and bury plastic bags containing tissue specimens in the dry ice. Cover the tissue / dry ice with the foam insulator. Remember to include completed patient data form. Seal shipping container and affix pre-printed shipping label.

Contact

Mark A. Watson M.D., Ph.D. Assistant Professor of Pathology Division of Laboratory Medicine / Box 8118 Washington University School of Medicine 660 S. Euclid Ave. St. Louis, MO. 63110

Phone: (314) 454-7919 Fax: (314) 454-5525

E-Mail: watsonm@labmed.wustl.edu

Appendix A

Bruce R. Korf, M.D., Ph.D.
Principal Investigator
Partners Center for Human Genetics
77 Avenue Louis Pasteur
Boston, MA 02115
617-525-5750 (Phone)
617-525-5757 (Fax)
bkorf@rics.bwh.harvard.edu

1

Jan Friedman, M.D., Ph.D.
Database
University of British Columbia
4500 Oak St.
Vancouver, BC
(604) 875-3489 (Phone)
(604) 875-2376 (Fax)
frid@unixg.ubc.ca

David Gutmann, M.D., Ph.D.
Tissue Bank
Washington University School of Medicine
660 S. Euclid Ave.
St. Louis, MO 63110
(314) 747-2055 (Phone)
(314) 362-9462 (Fax)
gutmannd@neuro.wustl.edu

Mia MacCollin, M.D., Ph.D. Clinical Center Massachusetts General Hospital Bldg 149, 13th St., Boston, MA 02129 (617) 726-5724 (Phone) (617) 726-5736 (Fax) maccollin@ helix.mgh.harvard.edu

Roger Packer, M.D. Clinical Center Children's National Medical Center 111 Michigan Ave. NW Washington, D.C. 20010 (202) 884-2120 (Phone) (202) 884-5226 (Fax) rpacker@cnmc.org Frank Liebermann, M.D.
Clinical Center
Mt. Sinai School of Medicine
1 Gustave Levy Place
New York, NY 10029
(212) 241-7581 (Phone)
(212) 987-3301 (Fax)
flieberman@smtplink.mssm.edu

David Viskochil, M.D., Ph.D. Clinical Center University of Utah, School of Medicine Division of Medical Genetics 413 MREB 50 N. Medical Dr. Salt Lake City, UT 84112 801-581-8943 (Phone) 801-585-5241 (Fax) dave.viskochil@hsc.utah.edu

Sharon Plon, M.D., Ph.D. Clinical Center Texas Children's Hospital Division of Hematology-Oncology 6621 Fannin St., 3-3320 Houston, TX 77030 (713) 770-4251 (Phone) (713) 770-4202 (Fax) splon@bcm.tmc.edu

Robert Hopkins, M.D. Clinical Center Children's Hospital Medical Center 3333 Burnet Ave., Cincinnati, OH 45229-2899 (513) 636-4471 (Phone) (513) 559-7297 (Fax) HOPKR0@CHMCC.ORG Susan Huson, M.D.
Clinical Center
Oxford University
Department of Clinical Genetics
Churchill Hospital
Headington, Oxford, UK
0X3 7LJ
+44 1 865 226 020 (Phone)
+44 1-865-226-01 (Fax)
susan.huson@clinical-medicine.oxford.ac.uk

Rosalie Ferner, M.D.
Clinical Center
Guys Hospital
St. Thomas' St.
London, UK
SE1 9RT
+44 171 955-4398 (Phone)
+44 171-955-4814 (Fax)
r.ferner@umds.ac.uk

Eric Legius, M.D.
Clinical Center
University of Leuven
Kon Elisabethlaan 20
Leuven B-3000 Belgium
+32 (16) 345-860 (Phone)
+32 (16) 345-997 (Fax)
eric.legius@med.kuleuven.ac.be

Victor-Felix Mautner, M.D. Clinical Center Klinikum Nord Ochsenzoll Langenhorner Chaussee 560 22419 Hamburg, Germany 49-40-5271-2872 (Phone) 49-40-5277-462 (Fax) VRGes@aol.com Kathryn North, M.D. Clinical Center Royal Alexandra Hospital PO Box 3515 Parramatta, NSW 2124 Australia 612 9845-3011 (Phone) 612 9845 3082 (Fax) kathryn@nch.edu.au

Fernando Kok, M.D.
Clinical Center
University of Sao Paulo
de Grendo Juliete 233
04721060
Sao Paulo, Brazil
55 11 521-2208 (Phone)
55 11 521-2208 (Fax)
Fernando.Kok@fleury.com.br

Joel Charrow, M.D., Ph.D. Clinical Center Children's Memorial Hospital 2300 Children's Plaza Chicago, IL 60614 773-880-4462 (Phone) 773-929-9565 (Fax) jcharrow@new.edu

John J. Mulvihill, M.D. Clinical Center Children's Hospital of Oklahoma 940 NE 13th St., Room 2418 Oklahoma City, OK 73104 405-271-8685 (Phone) 405-271-8697 (Fax) john-mulvihill@ouhsc.edu

Appendix B

CHILDREN'S HOSPITAL BOSTON, MASSACHUSETTS ADULT PARTICIPANT INFORMED CONSENT

Participant's Name:	Date:
Project Title: Natural History of Plexiform Neurofibromas Protocol Number: 97-12-239	
(Dates are modified by the Clinical Investigation Of	

DESCRIPTION AND EXPLANATION OF PROCEDURE:

We are asking for your consent for you to participate in a research study of the rate of growth of plexiform neurofibromas. Plexiform neurofibromas are a particular type of benign tumor that occurs in persons with neurofibromatosis type 1. The growth patterns of these tumors appear to be unpredictable and the factors that influence that growth are largely unknown. The goal of this study is to closely monitor the growth of plexiform neurofibromas for a period of at least three years using magnetic resonance imaging (MRI). This technique will permit us to measure the overall size (volume) of the plexiform neurofibroma. By repeating the assessment every 6-24 months we hope to be able to document the rate of change in size of the plexiform neurofibroma. This is part of an international study in which 300 individuals with NF1 will be enrolled; here at Children's Hospital we plan to enroll approximately 20 – 30 people.

Participation in this study will involve both clinical assessment and MRI scanning. The clinical assessment will occur every six months for three years. This will take place at Children's Hospital on Fegan 10 in the Neurofibromatosis Clinic. A standard physical examination will be done, the same as for a standard clinic visit. If the plexiform neurofibroma is visible on the surface it will be measured with a ruler or tape measure and photographs will be taken. Since these visits are deemed part of your clinical care, they will be billed to your medical insurance as standard clinical visits. A clinic note will be placed in the medical record and copies sent to your primary care provider, as is standard in the clinic. Data about your clinical assessment will be entered into a computer database. This clinical data is also sent to a central database maintained by the University of British Columbia, sponsored by the National Neurofibromatosis Foundation. You will be identified in this central database only by a code number, but not by name, to preserve confidentiality. Photographs of your plexiform neurofibroma will be kept in a confidential file in the Division of Genetics. Clinic visits will occur over a period of 30-45 minutes.

At the time of the first clinic visit when this study begins a blood sample will be obtained from you. The blood sample will be drawn from a vein in the arm, and will consist of approximately 5 - 10 cc (1 - 2 teaspoons). This sample will be used as a source of DNA, the genetic material inside our cells. We will also obtain serum (the liquid component of blood). This DNA and serum will be sent to a central tissue repository at Washington University in St. Louis and banked there. There are no immediate plans to study this DNA and serum, but at some point in the future it may be possible to examine the DNA for the changes in the NF1 gene, or in other genes that may alter the behavior of neurofibromas. The serum may be used to test for substances in the blood that cause neurofibromas to grow. Since we will be monitoring the growth of the neurofibroma carefully, we hope to have the opportunity to examine genetic or serum factors that may influence tumor growth at some point in the future. There is no assurance, however, that such testing will be possible or necessarily will be done. Any results obtained from DNA or serum studies will be kept confidential. You will have the opportunity to designate whether you would like to learn the results of such testing in the future, and whether you would like us to share these results with any health providers whom you designate. You can direct us to withdraw the blood sample from the repository at any time.

MRI scanning of the plexiform neurofibroma will be part of this study. Every participant will have an MRI at the time of enrollment into the study (unless the plexiform neurofibroma has been followed by MRI for a period of time before the study and is known to have not changed in size). A second MRI will be done one year later unless there are clinical reasons to do it sooner. MRI will be repeated at the end of the study, at three years. If the neurofibroma appears to be growing, either based on clinical assessment or from measurements of the MRI scans, follow-up MRI may be done more often, at the discretion of your physician, in accordance with standard clinical care.

In most cases these MRI scans are used in standard clinical care and will therefore be billed to your insurance. There may be some instances in which an MRI might not have been performed for routine clinical purposes at the same time as designated by the study. In these cases, funds are available to defray the costs of the MRI scan. In some instances it will be necessary to use sedation or general anesthesia. Consent for this procedure will be obtained by the radiologist or anesthesiologist prior to the procedure. Also, in some cases, it will be necessary to insert an intravenous line and administer contrast material into the vein. This will be done at the discretion of the radiologist, if it appears that contrast is necessary to better visualize the neurofibroma. Your consent will be obtained prior to this procedure. We expect that the MRI scans will require approximately one hour.

We do not plan to perform surgery or take a sample of the plexiform neurofibroma as part of this study, but in some cases surgery may be performed because of clinical indications. This decision will not be influenced by your participation in the study, and will not affect your participation in the study. If there is neurofibroma tissue available that is not needed for examination as part of clinical care, this tissue will be collected and sent to a central tissue bank at Washington University in St. Louis. In addition, a sample will be sent to Mt. Sinai School of Medicine for review of the pathological features of the neurofibroma. The tissue will be identified with a code number, and will only be possible to connect with your name through our clinic. The tissue may be distributed to investigators to help with their research on neurofibromatosis. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. It is not anticipated that results of study of your neurofibroma tissue will influence clinical management, and therefore you will not be informed of research results on this tissue. All research results will be kept confidential. You can withdraw your specimen from the tissue repository at any time.

RISKS AND DISCOMFORTS:

- 1. Clinical Assessment: The clinical assessments will be the standard ones performed in our Neurofibromatosis Clinic, with the addition of measurement of any visible plexiform neurofibroma. This assessment may cause some embarrassment, anxiety, and inconvenience. We will make every effort to insure that the clinic visits occur in an efficient and dignified manner, and will make every effort to explain what is being done and what is found. The clinic visits will be billed as standard clinical assessments. We will obtain prior approval from your insurance company and to explain that clinical follow-up of plexiform neurofibromas is appropriate clinical care.
- 2. Photography of Plexiform Neurofibromas: The photographs will be taken only of the region of your body affected by the plexiform neurofibroma. These photographs will be kept in a confidential file and will not contain your name. In some cases they may be used for teaching purposes or in scientific or medical publications related to this work, however.
- 3. Clinical Database: The clinical database is kept on a computer in a password-protected file. There is a potential risk of your clinical information being read by unauthorized persons, although the use of a password system should minimize this risk. To preserve your privacy, any data sent to the central database will be sent without any personal identifying information. You will be identified in the central database only by a code number, and our clinic will be the only place where the code number can be linked to your name.
- 4. Blood Sampling: The blood sampling procedure involves insertion of a needle into a vein in the arm and withdrawing 5 10 cc of blood (1 2 teaspoons). We expect to take no more than 10 cc (2 teaspoons) from adults. There is discomfort associated with blood drawing, and very slight risk of infection due to insertion of the needle. There is also risk of redness, bruising, and swelling

at the site from which the blood is removed. Blood will be drawn in the Children's Hospital phlebotomy (blood drawing) center, and every effort will be made to minimize the pain and to obtain the blood using sterile procedures.

- 5. Genetic Studies: Although there is no immediate plan to perform genetic studies from the blood samples obtained, genetic material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that DNA samples will be stored indefinitely in this repository. The sample will be identified by a code number that can be traced to you only by contact with our clinic. Genetic testing may eventually reveal the neurofibromatosis gene mutation that is responsible for NF1 in you. Although genetic testing can, in some cases, result in discrimination for health or life insurance or employment, we believe that these risks are minimal since it is already known that you have neurofibromatosis. It may also be possible to examine other genes that may influence the growth of neurofibromas in persons with NF1. Some of these may be genes that themselves can have implications for health. You will be given an opportunity to indicate whether you wish to know about any results that may be obtained, and whether you would like us to share these results with your health provider. We will keep all results confidential, however, and not disclose them to any other individual without your permission.
- 6. Tumor Studies: Tumor material will be obtained only if surgery is indicated for clinical reasons, and only after the pathologist and surgeon have determined that any material necessary for clinical care has been obtained. We will not ask that additional tumor material be obtained solely for research purposes, and will confine any tissue saved for research purposes to any excess tumor available after clinical studies are completed. Although there is no immediate plan to perform studies from any tumor samples obtained, tumor material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that the tissue samples will be stored indefinitely in the repository. The sample will be identified by a code number that can be traced to you only by contact with our clinic. No results will be placed in your medical record or disclosed to anyone without your permission.
- 7. MRI: Magnetic resonance imaging (MRI) is a standard procedure used for imaging plexiform neurofibromas. There are no known or foreseeable risks associated with exposures to MRI provided no metal implanted prostheses (e.g., vascular clamps or pacemakers; braces are not a problem). All potential subjects will be screened for the presence of such prior to the examination. Some participants in the study may require sedation or anesthesia to perform MRI. Consent for this will be obtained prior to the study. It must be recognized that there are risks associated with sedation and

anesthesia, including the risk of death in rare instances. The MRI scans and sedation/anesthesia costs will be billed to insurance.

POTENTIAL BENEFITS:

This study is being performed in conjunction with routine clinical care. It is standard to see individuals with neurofibromatosis in clinic at least once per year and more often if there is a problem such as plexiform neurofibroma. MRI imaging of plexiform neurofibromas is also done as part of standard clinical care. It is possible that, in the course of this study, growth of a plexiform neurofibroma will be discovered that requires further treatment, most likely surgical. In that case, referral to a surgeon who is familiar with the management of plexiform neurofibromas will be made. The MRI data in this study will be analyzed by a special approach called "volumetric MRI," in addition to being read in a standard manner by a radiologist. It is expected that the volumetric MRI approach will provide more precise measurement of the size of plexiform neurofibromas, and therefore will give more complete and objective information on which to base any possible future treatment decisions. Volumetric MRI is currently not available on a routine clinical basis.

ALTERNATIVES:

If you chose not to participate in this study, it will not influence your care or management in the Neurofibromatosis Program. It may be deemed necessary for you to have routine clinical assessments for a plexiform neurofibroma, which may include MRI scanning, but this will be done outside the context of the research study if you choose. This means that the data will not be shared with the central data facility and that DNA and potential tumor samples will not be obtained. Otherwise your care will be the same.

VOLUNTEER REGISTRY DATA BASE REQUIREMENTS:

This study is supported by the U.S. Army. It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number (if US Citizen), study name, and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risk and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

MEDICAL CARE FOR RESEARCH RELATED INJURY:

Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

REVIEW OF RESEARCH RECORDS:

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

CONSENT:	
performance. I have answered ability. I will inform the participations	Participant ed procedures and the risks involved in their and will answer all questions to the best of my ant of any changes in the procedures or the risks in during or after the course of the study. I have in to the subject.
 Date	Investigator's and/or Associate's Signature

CONSENT:

I have been satisfactorily informed of the above-described procedure and with its possible risks and benefits. I give permission for my participation in this study. I know that Dr. Korf or his associates may be reached at (617) 355-6394 and will be available to answer any questions that I may have. If I have questions regarding my rights as a research subject or questions regarding compensation in the event of a research related injury, I may request to speak with a member of the Hospital Consent Committee by calling (617) 355-7052. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect my care. I have been given a copy of this form.

Version 3/February 11, 1999

I understand that there is a possibility that the blood, tissue, body fluid, or sample(s) of neurofibroma tissue that I am providing under this study may also be used in other research studies and could potentially have some commercial applicability.

	Date	Signature of Patient/Participant
Name of Participant		
Address of Participant		
	Date	Witness to Signatures
Name of Witness	As a second seco	
Address of Witness		

6/14/99

Disclosure of Information Obtained from Genetic Studies

Please indicate whether you wish to be informed of any results of genetic studies that may be relevant to your health or to genetic counseling of you or your family:

I wish to be informed of the results of any genetic tests performed on my/my child's blood or tumor tissue that may have implications for health care or genetic counseling.

I do not wish to be informed.

Please indicate the name and address of any health provider to whom you would like any results sent.

Name:		 	
Address:	<u> </u>		
City:			

Zip:

6/14/99

State:

Sample Donation Form

Natural History of Plexiform Neurofibromas in NF1

I voluntarily and freely donate any and all blood, tissues, body fluid, product, or sample(s) of neurofibromas to Children's Hospital and hereby relinquish all right, title, and interest to said items.

_	Date	Signature of Patient/Participant
Name of Participant		
Address of Participan	t	
-	Date	Witness to Signatures
Name of Witness		
Address of Witness		

6/14/99

CHILDREN'S HOSPITAL BOSTON, MASSACHUSETTS CHILD PARTICIPANT INFORMED CONSENT

Participant's Name:	_ Date:
Project Title: Natural History of Plexiform Neurofibromas	
Protocol Number: 97-12-239	
(Dates are modified by the Clinical Investigation Office onl	y.)
Consent Form Valid from June 14, 1999 through June 13, 2000	

DESCRIPTION AND EXPLANATION OF PROCEDURE:

1

We are asking for your consent for your child to participate in a research study of the rate of growth of plexiform neurofibromas. Plexiform neurofibromas are a particular type of benign tumor that occurs in persons with neurofibromatosis type 1. The growth patterns of these tumors appear to be unpredictable and the factors that influence that growth are largely unknown. The goal of this study is to closely monitor the growth of plexiform neurofibromas for a period of at least three years using magnetic resonance imaging (MRI). This technique will permit us to measure the overall size (volume) of the plexiform neurofibroma. By repeating the assessment every 6-24 months we hope to be able to document the rate of change in size of the plexiform neurofibroma. This is part of an international study in which 300 individuals with NF1 will be enrolled; here at Children's Hospital we plan to enroll approximately 20 – 30 people.

Participation in this study will involve both clinical assessment and MRI scanning. The clinical assessment will occur every six months for three years. This will take place at Children's Hospital on Fegan 10 in the Neurofibromatosis Clinic. A standard physical examination will be done, the same as for a standard clinic visit. If the plexiform neurofibroma is visible on the surface it will be measured with a ruler or tape measure and photographs will be taken. Since these visits are deemed part of your child's clinical care, they will be billed to your child's medical insurance as standard clinical visits. A clinic note will be placed in the medical record and copies sent to your child's primary care provider, as is standard in the clinic. Data about your clinical assessment will be entered into a computer database on a computer in the Division of Genetics. This clinical data is also sent to a central database maintained by the University of British Columbia, sponsored by the National Neurofibromatosis Foundation. Your child will be identified in this central database only by a code number, but not by name, to preserve confidentiality. Photographs of your child's plexiform neurofibroma will be kept in a confidential file in the Division of Genetics. Clinic visits will occur over a period of 30-45 minutes.

At the time of the first clinic visit when this study begins a blood sample will be obtained from the study participant (i.e., your child). The blood sample will be drawn from a vein in the arm, and will consist of approximately 5-10 cc (1 - 2 teaspoons). This sample will be used as a source of DNA, the genetic material inside our cells. We will also obtain serum (the liquid component of blood). This DNA and serum will be sent to a central tissue repository at Washington University in St. Louis and banked there. There are no immediate plans to study this DNA and serum, but at some point in the future it may be possible to examine the DNA for the changes in the NF1 gene, or in other genes that may alter the behavior of neurofibromas. The serum may be used to test for substances in the blood that cause neurofibromas to grow. Since we will be monitoring the growth of the neurofibroma carefully, we hope to have the opportunity to examine genetic or serum factors that may influence tumor growth at some point in the future. There is no assurance, however, that such testing will be possible or necessarily will be done. Any results obtained from DNA or serum studies will be kept confidential. You will have the opportunity to designate whether you would like to learn the results of such testing in the future, and whether you would like us to share these results with any health providers whom you designate. You can direct us to withdraw the blood sample from the repository at any time.

MRI scanning of the plexiform neurofibroma will be part of this study. Every participant will have an MRI at the time of enrollment into the study (unless the plexiform neurofibroma has been followed by MRI for a period of time before the study and is known to have not changed in size). A second MRI will be done one year later unless there are clinical reasons to do it sooner. MRI will be repeated at the end of the study, at three years. If the neurofibroma appears to be growing, either based on clinical assessment or from measurements of the MRI scans, follow-up MRI may be done more often, at the discretion of your child's physician, in accordance with standard clinical care.

In most cases these MRI scans are used in standard clinical care and will therefore be billed to your child's insurance. There may be some instances in which an MRI might not have been performed for routine clinical purposes at the same time as designated by the study. In these cases, funds are available to defray the costs of the MRI scan. In some instances, particularly for small children, it will be necessary to use sedation or general anesthesia. Consent for this procedure will be obtained by the radiologist or anesthesiologist prior to the procedure. Also, in some cases, it will be necessary to insert an intravenous line and administer contrast material into the vein. This will be done at the discretion of the radiologist, if it appears that contrast is necessary to better visualize the neurofibroma. Your consent will be obtained prior to this procedure. We expect that the MRI scans will require approximately one hour.

We do not plan to perform surgery or take a sample of the plexiform neurofibroma as part of this study, but in some cases surgery may be performed because of clinical indications. This decision will not be influenced by your child's participation in the study, and will not affect your child's participation in the study. If there is neurofibroma tissue available that is not needed for examination as part of clinical care, this tissue will be collected and sent to a central tissue bank at Washington University in St. Louis. In addition, a sample will be sent to Mt. Sinai School of Medicine for review of the pathological features of the neurofibroma. The tissue will be identified with a code number, and will only be possible to connect with your name through our clinic. The tissue may be distributed to investigators to help with their research on neurofibromatosis. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. It is not anticipated that results of study of your neurofibroma tissue will influence clinical management, and therefore you will not be informed of research results on this tissue. All research results will be kept confidential. You can withdraw your specimen from the tissue repository at any time.

RISKS AND DISCOMFORTS:

- 8. Clinical Assessment: The clinical assessments will be the standard ones performed in our Neurofibromatosis Clinic, with the addition of measurement of any visible plexiform neurofibroma. This assessment may cause some embarrassment, anxiety, and inconvenience. We will make every effort to insure that the clinic visits occur in an efficient and dignified manner, and will make every effort to explain what is being done and what is found. The clinic visits will be billed as standard clinical assessments. We will obtain prior approval from your child's insurance company and to explain that clinical follow-up of plexiform neurofibromas is appropriate clinical care.
- 9. Photography of Plexiform Neurofibromas: The photographs will be taken only of the region of your child's body affected by the plexiform neurofibroma. These photographs will be kept in a confidential file and will not contain your child's name. In some cases they may be used for teaching purposes or in scientific or medical publications related to this work, however.
- 10. Clinical Database: The clinical database is kept on a computer in a password-protected file. There is a potential risk of your clinical information being read by unauthorized persons, although the use of a password system should minimize this risk. To preserve your child's privacy, any data sent to the central database will be sent without any personal identifying information. Your child will be identified in the central database only by a code number, and our clinic will be the only place where the code number can be linked to your child's name.

- 11. Blood Sampling: The blood sampling procedure involves insertion of a needle into a vein in the arm and withdrawing 5 10 cc of blood (1 2 teaspoons). We expect to take only 5 cc (1 teaspoon) from children under five years of age and no more than 10 cc (2 teaspoons) from children over five years of age or from adults. There is discomfort associated with blood drawing, and very slight risk of infection due to insertion of the needle. There is also risk of redness, bruising, and swelling at the site from which the blood is removed. Blood will be drawn in the Children's Hospital phlebotomy (blood drawing) center, and every effort will be made to minimize the pain and to obtain the blood using sterile procedures.
- 12. Genetic Studies: Although there is no immediate plan to perform genetic studies from the blood samples obtained, genetic material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that DNA samples will be stored indefinitely in this repository. The sample will be identified by a code number that can be traced to your child only by contact with our clinic. Genetic testing may eventually reveal the neurofibromatosis gene mutation that is responsible for NF1 in your child. Although genetic testing can, in some cases, result in discrimination for health or life insurance or employment, we believe that these risks are minimal since it is already known that your child has neurofibromatosis. It may also be possible to examine other genes that may influence the growth of neurofibromas in persons with NF1. Some of these may be genes that themselves can have implications for health. You will be given an opportunity to indicate whether you wish to know about any results that may be obtained, and whether you would like us to share these results with your child's health provider. We will keep all results confidential, however, and not disclose them to any other individual without your permission.
- 13. Tumor Studies: Tumor material will be obtained only if surgery is indicated for clinical reasons, and only after the pathologist and surgeon have determined that any material necessary for clinical care has been obtained. We will not ask that additional tumor material be obtained solely for research purposes, and will confine any tissue saved for research purposes to any excess tumor available after clinical studies are completed. Although there is no immediate plan to perform studies from any tumor samples obtained, tumor material will be stored for possible future testing. The storage will take place in a tissue repository at Washington University in St. Louis. It is expected that the tissue samples will be stored indefinitely in the repository. The sample will be identified by a code number that can be traced to your child only by contact with our clinic. No results will be placed in your medical record or disclosed to anyone without your permission.
- 14.MRI: Magnetic resonance imaging (MRI) is a standard procedure used for imaging plexiform neurofibromas. There are no known or foreseeable risks

associated with exposures to MRI provided no metal implanted prostheses (e.g., vascular clamps or pacemakers; braces are not a problem). All potential subjects will be screened for the presence of such prior to the examination. Some participants in the study may require sedation or anesthesia to perform MRI. Consent for this will be obtained prior to the study. It must be recognized that there are risks associated with sedation and anesthesia, including the risk of death in rare instances. The MRI scans and sedation/anesthesia costs will be billed to insurance.

POTENTIAL BENEFITS:

:

This study is being performed in conjunction with routine clinical care. It is standard to see individuals with neurofibromatosis in clinic at least once per year and more often if there is a problem such as plexiform neurofibroma. MRI imaging of plexiform neurofibromas is also done as part of standard clinical care. It is possible that, in the course of this study, growth of a plexiform neurofibroma will be discovered that requires further treatment, most likely surgical. In that case, referral to a surgeon who is familiar with the management of plexiform neurofibromas will be made. The MRI data in this study will be analyzed by a special approach called "volumetric MRI," in addition to being read in a standard manner by a radiologist. It is expected that the volumetric MRI approach will provide more precise measurement of the size of plexiform neurofibromas, and therefore will give more complete and objective information on which to base any possible future treatment decisions. Volumetric MRI is currently not available on a routine clinical basis.

ALTERNATIVES:

If you chose not to have your child participate in this study, it will not influence your child's care or management in the Neurofibromatosis Program. It may be deemed necessary for your child to have routine clinical assessments for a plexiform neurofibroma, which may include MRI scanning, but this will be done outside the context of the research study if you choose. This means that the data will not be shared with the central data facility and that DNA and potential tumor samples will not be obtained. Otherwise your child's care will be the same.

VOLUNTEER REGISTRY DATA BASE REQUIREMENTS:

This study is supported by the U.S. Army. It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your child's name, address, Social Security number, study name, and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can

exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risk and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

MEDICAL CARE FOR RESEARCH RELATED INJURY:

Should your child be injured as a direct result of participating in this research project, your child will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your child's legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

REVIEW OF RESEARCH RECORDS:

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

<u>CONSENT</u> :	
I have fully explained to	the nature and
, .	Parent/guardian
performance. I have answered ability. I will inform the participal	d procedures and the risks involved in their and will answer all questions to the best of my nt of any changes in the procedures or the risks during or after the course of the study. I have to the family.
Date	Investigator's and/or Associate's Signature

CONSENT:

I have been satisfactorily informed of the above-described procedure and with its possible risks and benefits. I give permission for my child's participation in this study. I know that Dr. Korf or his associates may be reached at (617) 355-6394 and will be available to answer any questions that I may have. If I have questions regarding my child's rights as a research subject or questions regarding compensation in the event of a research related injury, I may request to speak with a member of the Hospital Consent Committee by calling (617) 355-7052. I understand that I am free to withdraw this consent and discontinue participation in this project at any time, even after signing this form, and it will not affect my child's care. I have been given a copy of this form.

I understand that there is a possibility that the blood, tissue, body fluid, or sample(s) of neurofibroma tissue that I am providing under this study may also be used in other research studies and could potentially have some commercial applicability.

	Date	Signature of Parent/Guardian
Name of Parent/Gua	ardian	
Address		
	Date	Witness to Signatures
Name of Witness		
Address of Witness		

6/14/99

1

Disclosure of Information Obtained from Genetic Studies

Please indicate whether you wish to be informed of any results of genetic studies that may be relevant to your health or to genetic counseling of you or your family:

I wish to be informed of the results of any genetic tests performed on my/my child's blood or tumor tissue that may have implications for health care or genetic counseling.

I do not wish to be informed.

Please indicate the name and address of any health provider to whom you would like any results sent.

Name:	 		
Address:			
City:		. AV	
State:	Zip:		

6/14/99

Sample Donation Form

Natural History of Plexiform Neurofibromas in NF1

I voluntarily and freely donate any and all blood, tissues, body fluid, product, or sample(s) of neurofibromas to Children's Hospital and hereby relinquish all right, title, and interest to said items.

_	Date	Signature of Parent
Name of Participant		
Address of Participan	t	
_	Date	Witness to Signatures
Name of Witness Address of Witness		

6/14/99

. 3

Appendix C

. .

VOLUNTEER REGISTRY DATA SHEET

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

- 1. AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397
- 2. Principal and Routine Purposes: To document participation in research conducted or sponsored by the U.S. Army Medical Research and Materiel Command. Personal information will be used for identification and location of participants.
- Mandatory or Voluntary Disclosure: The furnishing of the SSN is mandatory and necessary to provide identification and to
 contact you if future information indicates that your health may be adversely affected. Failure to provide information may preclude your
 participation in the research study.

PART A - INVESTIGATOR INFORMATION

(To Be Completed By Investigator)

(City) ermanent Home Address (Home Address) (City) ermanent Home Phone Number:	(Country)	(P.O. Box / Apar (State) (P.O. Box / Apa (State)	
(Street) (City) ermanent Home Phone Number: 4. * Local Address (If Different F (Street)	(Country) (Country) (Country)	(P.O. Box / Apar (State)	(Zip Code)
(Street) (City) ermanent Home Phone Number: 4. * Local Address (If Different F	(Country)	(P.O. Box / Apar (State)	(Zip Code)
(Street) (City) ermanent Home Phone Number:	ome of Record) or Study Location: (Country)	(P.O. Box / Apar (State)	tment Number) (Zip Code)
3. Permanent Home Address (Ho (Street) (City) ermanent Home Phone Number: _	ome of Record) or Study Location: (Country)	(P.O. Box / Apar (State)	tment Number)
3. Permanent Home Address (Ho (Street)	ome of Record) or Study Location:	(P.O. Box / Apar (State)	tment Number)
3. Permanent Home Address (Ho	ome of Record) or Study Location:	(P.O. Box / Apar	tment Number)
3. Permanent Home Address (Ho			
3. Permanent Home Address (Ho			
LEASE PRINT, USING INK OR	(To Be Completed By Vol BALLPOINT PEN 8. Name:	lunteer)	
	PART B - VOLUNTEER IN	FORMATION	
3.			
2.			
DD M. Principal / Other Investigator(s			n / Laboratory
. Contractor (Laboratory / Instit	toute Conducting Student		
	2. Protocol Title:		
Study Number:	2 Protocol Titles		

(To Be Completed By Investigator)

Did volunteer finish participation: Y: N: If YES, date finished	1 1
Did volunteer linish participation: 1: N: II 123, date linished	DD MM YY
If NO, date withdrawn:/ Reaso	n Withdrawn:
B. Did any Serious or Unexpected Adverse Incident or Reaction Occur: Y:	N: If YES, Explain:
9. * Volunteer Follow-up:	
Purpose:	
Date:/ Was contact made: Y:	N: If no action taken, explain
). * Hard Copy Records Retired: Place:	File NR:
. * Product Information:	
Product:	
Manufacturer:	
Manufacturer: Expiration Date:	

When completed, a copy of this form should be sent to the address below:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
Fort Detrick, MD 21702-5012

Appendix D

Patient Registration Form

Natural History of Plexiform Neurofibromas in NF1

Fax this form to Mary Sanford at Children's Hospital, **(617) 355-7588**. Please call (617) 355-3479 if there are problems with fax transmission.

Institution	
Physician	
Fax	
Patient Information	
	Please refer to the instructions in the
Database ID #	Procedures and Policies Manual
Age	
Sex M F	
Plexiform Site (Check One) Head and Ne	ck
Refer to Manual for Definitions Trunk and Li	mbs (externally visible)
Trunk and Li	mbs (internal)
Prior Surgery Y N If yes, D.	ATE
Diagnostic Criteria	
Six or more <i>café-au lait-</i> macules	
Freckling in the axillary or inguinal r	egion
Neurofibromas	
Lisch nodules	
Optic glioma	
Tibial or orbital dysplasia	
Family History	
To be completed by Children's Hospital only:	
To be completed by Children's Hospital Only.	脚準には、アーザとは17~ 「代発理館財政で置ければ」」。 「大海盗会」とおよりより女会は日本の場合して
Natural History of Plexiform Neurofibromas in NF1 ID#:	
Vec. We will include this nations in the church	of Netural History of Playiform
Yes, We will include this patient in the stud Neurofibromas in NF1. Please refer to the	
No, Unfortunately this patient does not mee	t the needs of this study.

Approved by: _

Date Reviewed:

Appendix E

Patient Withdrawal Form

Natural History of Plexiform Neurofibromas in NF1

Fax this form to Mary Sanford at Children's Hospital, **(617) 355-7588**. Please call **(617) 355-3479** if there are problems with fax transmission.

Date					
Institution		 			
NF Patient ID#		 			
Reasons for Wit	hdrawal:				
				,	

Physician Signature

Date

Appendix F

Adverse Events Form

Natural History of Plexiform Neurofibromas in NF1

Fax this form to Mary Sanford at Children's Hospital, **(617) 355-7588**. Please call **(617) 355-3479** if there are problems with fax transmission.

Date			
Institution			
NF Patient ID#			
Date of Visit		_ _	
Description of A	dverse Events:		

Physician Signature

Date

Appendix G

NNFF International Database - 1999 Update

The database now contains clinical information on approximately 4000 individuals with NF, collected at over 30 centers throughout the world. Any NF clinic is welcome to contribute to, and obtain data from, this resource.

We have updated the database to allow data entry via the Internet and/or via scannable paper forms, although the existing DOS-based system will still remain an option. We have also redesigned the database to consist of 7 demographic questions, 25 core NF questions, and optional modules designed to record detailed information for each of the following specialities: dermatology, ophthalmology, neurology, psychology/cognitive development, endocrinology, dysmorphology, and orthopaedics.

Scannable Forms

The scannable paper forms are enclosed. As you can see, they are mostly multiple choice, and they have an area to record notes, pedigrees or diagrams. When they are scanned into the computer, the multiple-choice questions are recorded in the database and the notes and diagrams are stored as a graphic image. Optical character recognition software allows hand-written numbers, such as date of visit, and head circumference, to be stored in the database.

To date, the scannable forms are available only for the demographic and core questions. We will design and implement the optional modules if there is a demand for this system.

Paper forms were chosen because they enable data entry to occur during a clinic visit and may become part of the permanent clinic record. Scanning data into the computer avoids the time required to manually enter data as well as avoiding most data entry errors. Another major advantage of the paper forms is that they may be translated into any language. You may use the forms immediately. Please photocopy as many as you need for your clinic.

Web Data Entry

Our new web version of the database contains the same demographic questions, core questions and optional modules as described above. This data entry system is designed to be as rapid as possible via the Internet. Clinics will be able to add and edit data for their own patients and will also have read-only access to clinical data for all other patients on the database. A sophisticated search procedure will allow authorised clinicians to perform database searches.

Information on accessing the web version of these forms appears on a separate sheet along with the web address, your user name and password. The best way to get to know this program is to try it out but we are available for questions:

Email: birch@interchg.ubc.ca,

Phone: 604-822-5348 Fax: 604-822-2749

Mail: U.B.C. Dept. of Medical Genetics,

222-6174 University Blvd., Vancouver, B.C. V6T 1Z3

Canada

Using the Scannable Forms

Enclosed are copies of the Demographic Form and Core Questions. These are the questions that are obligatory in the revised database.

If you would like to contribute data using these forms you may do so immediately. Please note that the forms are specifically coded for your centre. Don't use anyone else's forms!

The forms are "read" by a computer. This means that there are certain rules to follow:

- 1. For the multiple-choice options, please completely fill circles (for each choice) with a dark-coloured pen or pencil. Several of the questions (e.g. Ethnic Origin, on the Demographic Form) can accept more than one option per question. In these cases, complete as many as are necessary.
- 2. For the scannable data (database numbers, dates, height and head circumference), please print clearly, one number to each box. Avoid touching the box lines with your pen.

You may transmit the forms to us by fax, or you may mail them to me in batches. Please make sure that the forms for each patient stay together!

For more information, please do not hesitate to contact Patricia Birch, Database Coordinator:

Email: birch@interchg.ubc.ca,

Phone: 604-822-5348 Fax: 604-822-2749

Mail: U.B.C. Dept. of Medical Genetics,

222-6174 University Blvd., Vancouver, B.C. V6T 1Z3

Canada

Assigning a Database Number

If you have used the database before...

you will know that the database number consists of a three digit site number (which is pre-filled in the scannable forms); a four digit family number; and a three digit individual number. As before, you need to assign the family and individual numbers for each patient. If you have entered data via the old system, please continue with whatever method you now use to assign these numbers.

If you are new to the database,

you need to know that the database number consists of a three digit site number; a four digit family number; and a three digit individual number. You need to assign the family and individual numbers for each patient

Assigning a site number

The site number is assigned by us. Your site number is attached to your user name and is automatically filled in when you enter data by the web. If you are using the paper forms, the site number has been pre-filled for you.

Assigning family numbers

Start with family number "0001," and number each new family sequentially: "0002," "0003,"....

Assigning individual numbers

To assign an individual number, you may devise your own method, or you may choose one of two methods described below:

Method 1: Some centres number the proband "001" and number other family members sequentially: "002," "003,"...

Method 2: Other centres number the proband "500," and his or her generation sequentially: "501," "502," "503." The proband's children's generation are numbered starting with "600," "601," etc., and the proband's parent's generation are numbered starting with "400," "401," etc.

Names are not recorded on the database. This adds a level of confidentiality, but puts the onus on data contributors to keep track of the data they have entered. Keep a record in your own clinic of the family and individual numbers that you assign to patients. Without this, it will be very difficult to link the database number to your own patients!

Appendix H



Natural History of Plexiform Neurofibromas in NF1 NNFF International Database

		NF Date	ibase Num	ber		
		Plexiform (Study Num	ber		
Date	of Exam / / mont	/ day		Sex O Male O Female	Yea	r of Birth
	eneral info		n metient b	an bàd.		
O M O Pt O Bl	his visit, ind RI notograph Ta ood Sample ssue Specim	aken Taken	patient n	as nag:		
Clini	cal evidence	e of growtl	of plexifo	orm O Yes	ONo OUr	ncertain
MAL		<i>er Staging</i> O One	- See Prod	cedure Manua O Three		
FEM/		00	0140	O miee	O Four	O Five
	er Stage - P er Stage - B			O Three	O Four O Four	O Five
				Uncertain (· · · · ·
				O Not applie		
II. Pk	exiform S	tudy Gro	up			
	ad and Neck		_		•	
) Tru	nk and Limb	s (External	y Visible)			
	nk and Limb		•			



Plexiform Study Number

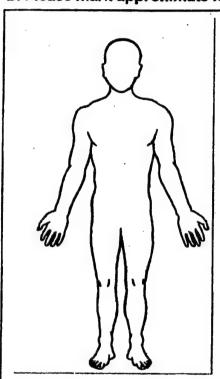
III. Location and Size

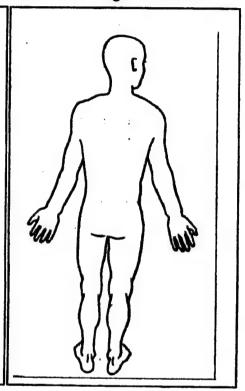
A. Please choose the area which best describes the location of the plexiform.

- O Head
- O Left Arm
- O Right Arm
- O Dorsal

- O Neck
- O Left Leg
- O Right Leg
- O Ventral

B. Please mark approximate location on the diagram below. .



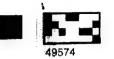


C. In the box below, you may draw the tumor, add multiple measurements, noting anatomical landmarks to ensure measurement consistency over time.



Plexiform Study	Number		
-----------------	--------	--	--

D. Externally Measureable O Yes O No
Diameter One mm
Diameter Two mm
Significant Production
IV. Appearance, Signs and Symptoms
A. Externally Visible O Yes O No
If YES, please answer the following questions. If NO go to Section V.
O Cutaneous Hyperpigmentation
O Cutaneous Hypertrophy
O Increased Skin Vascular Markings
O Decreased Skin Vascular Markings
O Palpable Mass
O Hair Growth from Tumor Site
B. Facial Involvement O Yes O No If YES, please answer the following questions. If NO go to Section IV.C. Eyes
Upper Lid O Left O Right
Lower Lid O Left O Right
Proptosis O Left O Right
Enophthalmomos O Left O Right
Glaucoma O Left O Right
Face
O Forehead '
O Cheek
O Nose
O Upper Lip
O Lower Lip
O Jaw
O Pre-auricular
O Pinna
O Post-auricular
O Tongue
O Upper Aveolar Ridge
O Lower Aveolar Ridge



NNFF International Database Demographic Questions

	3 1
alah yang manang magabad A	NF Database Number
	Local ID Number
1	Sex
	O Male
	O Female
2	Date of Birth
	year / month / day
·.	
3	Date of death
	year / month / day
4	Type of NF
	ONF 1
	O Possible NF1
	O Segmental NF1
	O Other Type (include Watson Syndrome)
	O NF2
	O Unknown
5	
	O New mutation
	O Mother affected
	O Father affected
	O Both parents affected O Unknown
	O UTKIOWII



6 Ethnic Origin

- O Asian Japanese
- O Asian Chinese
- O Asian Indian Subcontinent
- O Asian Other
- O Asian Unknown
- O Black
- O Latin American
- O Native American
- O White
- O Other
- O Unknown

7	Date	of	Exam
---	------	----	------

	/]/	
vear	/	month	/	day



NNFF International Database Core Questions

	NF Database Number	
1	Date of Exam year / month / day	
2	Height/length (leave blank if unknown) ft in	
3	Head Circumference	
4	Number of cafe au lait > 1.5 cm (> 0.5 cm pre-puberty) O None O 1 O 2 O 3 O 4	
	O 5 O 6 or more O Present, number unknown O Unknown	
5	Intertriginous Freckling O Absent O Present O Unknown	



6	Subcutaneous	neurofibromas
v	Subcutaneous	neuronoromas

- O None
- 01
- 02
- 03-9
- 0 10-50
- 0 > 50
- O Unknown

7 Cutaneous neurofibromas (including pendulous)

- O None
- 01
- 02
- 03-9
- 0 10-50
- 0 > 50
- O Unknown

8 Plexiform neurofibroma - Location (check as many as apply)

- O None
- O Orbit
- O Face
- O Head/neck
- O Trunk dorsal
- O Trunk ventral
- O Arm
- O Leg
- O Unknown

9 Paraspinal neurofibromas

- O Absent by scan
- O Absent clinically
- O Present
- O Unknown

10 Xanthogranulomas

- O Absent
- O Present
- O Unknown

11 Lisch nodules

- O Absent
- O Present on slit lamp example
- O Possible
- O Unknown



12 Proptosis

- O Absent
- O Unilateral
- O Bilateral
- O Present, laterality unknown
- O Unknown

13 Optic glioma

- O Absent by scan
- O Absent clinically
- O Present asymptomatic
- O Present symptomatic
- O Unknown

14 Seizures type

- O None
- O Febrile only
- O Hypsarrhythmla
- O Generalized
- O Partial
- O Multiple types
- O Present type unknown
- O Other
- O Unknown

15 Hydrocephalus

- O Absent clinically
- O Absent by scan
- O Aqueductal stenosis
- O Other non-communicating
- O Communicating
- O Present type unknown
- O Unknown

16 Intellectual Development

- O Normal
- O Mildly Delayed
- O Significantly Delayed
- O Unknown



17 Learning Problems

- O None
- O Specific learning problems present
- O Unknown

18 Hypertension

- O Absent
- O Present
- O Unknown

19 Congenital heart disease

- O Absent clinically
- O Absent by special testing
- O Aortic stenosIs
- OASD
- O Patent ductus arteriosis
- O Pulmonic stenosis
- O Tetralogy of Fallot
- O VSD
- O Other type of CHD
- O Multiple types of CHD
- O Possible CHD
- O Unknown

20 Vascular anomalies

- O Absent clinically
- O Renal artery stenosis
- O Arterial stenosis (non-renal)
- O Moya moya
- O Other
- O Unknown

21 Age puberty began

- 0<10
- O 10-15
- 0 > 15
- O Not Applicable
- O Unknown

• 5 0	590
22	Dysmorphic features

- O No
- O Yes
- O Possible
- O Unknown

23 Congenitally bowed tibia or pseudoarthrosis

- O Absent clinically
- O Absent radiographically
- O Present
- O Unknown

24 Dysplastic vertebrae

- O Absent clinically
- O Absent radiographically
- O Present
- O Unknown

25 Scollosis

- O Absent clinically
- O Absent radiographically
- O Present
- O Unknown

26 Dysplastic sphenoid wing

- O Absent clinically
- O Absent radiographically
- O Present bilateral
- O Present unilateral
- O Present laterality unknown
- O Unknown



27	Neoplasm	type
	HEODINGHI	LYPU

- O None
- O Carcinoma
- O Ependymona
- O Glioma
- O Leukemia
- O Lymphoma
- O Malignant peripheral nerve sheath tumour
- O Meningloangiomatosis
- O Meningioma
- O Pheochromocytoma
- O Sarcoma
- O Schwannoma
- O Malignancy present, type unknown
- O Other

20	0		-		
28	U	וווכ	Ш	en	เเธ

Appendix I

Male

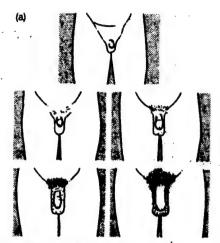


Fig. 10.2(a) Male genital development (G-1-G-5) and public hair (PH-5) to PH-5). Tanner stages. (From Tanner (1975), by permission.)

Female

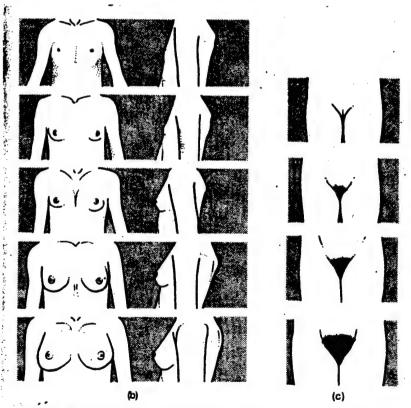


Fig. 10.2(b) Female breast development (B-1-B-5) and (c) pubic hair (PH-2 to PH-5). Tanner stages. (From Tanner (1975), by permission.)

Note: These illustrations were adapted from the Handbook of Normal Physical Measurements.

Appendix J

MRI Reimbursement Form

Natural History of Plexiform Neurofibromas in NF1

MRIs will be reimbursed at the your institution's *Research Rate*. Please check will your radiology or research departments for your institutions rate.

Date			
Institution			
MRI Research Rate			
NF Patient ID#			
Date of Visit	Date of Last	MRI	
Does the patient have insurance?	YES	NO	
If YES, reason for denial:			
Physician Signature		Date	
To be completed by Children's Hospital only:			
Date:			
We will reimburse you an	amount of \$	for the MRI.	
MRI is not necessary at th	is time.		

Appendix K

Form Completed By:	

Date: (Mo/D/Yr) ___/ __/ ___/



NF1 WorldCare Site Survey and Qualification Form

Information you enter here will be used to qualify your MRI site as a Patient Collection Center for participation in the NF2 Natural History Study. All information will be kept confidential.

Section 1 - MRI Site Contact Information

1.		ble for NF1 Natural History Study at this site:
	Name:	
	Position:	
	Email:	
	Phone #:	40.0
	Fax:	
	Address:	
	-	
	-	
2. 7	Name:	(scanner/network):
	Position:	
	Email:	
	Phone:	
	Fax:	
	Pager:	
Sec	ction 2 – MRI Sca	anner Information
3.	Name of MRI s	ite:
4.	Manufacturer (of MRI:
5.	Model Number	of MRI:
6.	Year MRI was	Purchased:

Form Completed By:	Date: (Mo/D/Yr)//
Section 3 - DICOM 3.0 Export Information	
7. Can Your MRI Export it's Image Data in a DICOM 3.0 Fo	ormat? Yes / No
If YES go to A and skip section 4. If No go to section 4.	
A. Does your machine act as a DICOM 3.0 Server?	Yes / No
B. Can your MRI DICOM 3.0 Server push data through a without being hindered by existing firewalls?	n Intranet via a dial up modem or an ISDN line
	Yes / No
C. Does your MRI machine push its DICOM 3.0 format to	another machine that acts as a DICOM 3.0 Server? $Yes \; / \; No$
D. Can that DICOM 3.0 Server push data through an Intr being hindered by existing firewalls?	anet via a dial up modem or an ISDN line without
	Yes / No
E. If your system is blocked by existing firewalls, are you a media?	able to output the DICOM 3.0 data to some sort of
	Yes / No
F. If yes what type of media?	
G. What is the manufacturer of the media? Please list mo	del numbers:
H. What is the manufacturer of the drive? Please list mod	del numbers:
I. Is there a host machine hooked to the drive? Please do	escribe:
J. Is there a Pioneer Optical Drive hooked to your system	n? es / No
K. If no, can a Pioneer Optical Drive be added?	es / No
Continue A. Altanua dina Ella Economica Información	
Section 4 – Alternative File Format Information 8. If your MRI Raw Data is not exported in DICOM 3.0 form	nat nlease list the specifications of the file format
	mi, preuse list the specifications of the fire format.
A. Does your MRI output to a server that understands the	format? Yes / No

Form Completed By:		Date: (Mo/D/Yr)//		
В.	Can that server push data through an Intranet via a hindered by existing firewalls?	dial up modem or an ISDN line without being		
		Yes / No		
C.	If your system is blocked by existing firewalls, are you	u able to output the data to some sort of media? $Yes \ / \ No$		
D.	If yes what type of media?			
E.	What is the manufacturer of the media? Please list	model numbers:		
F.	· · · · · · · · · · · · · · · · · · ·	nodel numbers:		
G.	Is there a host machine hooked to the drive? Please	describe:		
H	Is there a Pioneer Optical Drive hooked to your sys	tem? Yes / No		
I.	If no, can a Pioneer Optical Drive be added?	Yes / No		
Section 9. Co	n 5 – Additional Network and Software Information ommunications information for your scanner:			
	Network Interface Card:			
	IP:			
	Subnet mask:			
	Gateway:			
	DNS:			
10. D	ICOM 3.0 sources			
	First source:			
	Modality type:MRI_			
	Manufacturer/model:			
	Software Name, Rev #:			
	Second source (if any):			
	Modality type:			
	Manufacturer/model:			
	Software Name, Rev #:			



NF1 MRI Site Test Data Qualification Form

Th	is section to be completed by the MR	II site:		
1.	Name and title of person performing	ng test data transfer: _		
2.	Date of test data transfer:			
3.	What modality is the test data set?	OD /FTP	/ Other:	
4.	If optical disk (OD), what is the ma	nnufacturer and model	number?	
5.	Briefly describe the contents of the	test data set:		
_				
				,
Th	is section to be completed by the Wo	orldCare Measuremen	t Center:	
1.	Can the test data set received be co	onverted to DICOM 3.	0? Yes / No	
2.	Is the test data readable and the qu	uality of all images acc	eptable for image analysis?	Yes / No
3.	If NO, briefly describe the problem	ns with the test data se	t:	
			`	
Th in	ne undersigned WorldCare Measure accordance with NF2 WCMC Stand	ment Center represent lard Operating Proced	ative acknowledges that the test dures.	lata set is acceptable
_	Signature	Title	Date	

Appendix L

tudy#		Date of Scan
	NF1 MRI DATA	COLLECTION FORM
Го:	Mary Sanford	From:
Pax:	(617) 525 - 5757	Site:
Phone:	(617) 525 - 5758	Site Phone #:
Re:	Patient Collection Information	Site Fax #:
	MRI Acquisition Head and Neck Trunk and Extre Spine	on Protocol (Please choose one.) mities
	<u>Data '</u>	Transfer Information
	Date to transfer images:/_	
	Data Transmission Modality:	(optical disk or FTP)
		(if applicable)

SEND THIS FORM WITH APPROPRIATE ACQUISITION PROTOCOL FORM $\underline{\mathit{AND}}$ KEEP A COPY FOR YOUR RECORDS

Appendix M

NF Database ID#	Date of Scan
NF Study#	

NF1 ACQUISITION PROTOCOL

MRI PROTOCOL-HEAD/NECK

NOTE: ALL SERIES WITH THE EXCEPTION OF # 2 AND #3 SHOULD BE PERFORMED PER A NORMAL CLINICAL SCAN AS SPECIFIED BY THE RADIOLOGIST. THESE ADDITIONAL SERIES #2 AND #3 MAY OR MAY NOT BE PART OF THE NORMAL CLINICAL SCAN SEQUENCE, HOWEVER THESE SERIES ARE REQUIRED FOR THE NF1 STUDY PROTOCOL AND MUST BE PERFORMED WITHIN PROTOCOL SPECIFICATIONS AS INDICATED BELOW.

1.	SAGITTAL T1	PER NORMAL CLINICAL SCAN		
2.	AXIAL FSEIR • ECHO TRAIN LENGTH: 8	Protocol Specifications	Actual Specifications	Reason For Change
	TR	6000		
	 TE 	34		
	• TI	150		
	 SLICE THICKNESS 	4 MM		
	 SKIP 	0		
	 Matrix 	256 x 256		
	• FOV	22 CM		
	• NEX	1		
	Frequency Direction	A→P		
	 OPTIONS: TAILORED RF, FC, 0. 			
3.	CORONAL FSEIR			
	 ECHO TRAIN LENGTH: 8 			
	• TR	6000		
	• TE	34		
	• TI	150		
	 SLICE THICKNESS 	5 MM		
	• SKIP	0 MM		
	MATRIX	256 x 192		
	• FOV	22 CM		
	• NEX	1		
	 FREQUENCY DIRECTION 	S→I		
	 OPTIONS: TAILORED RF, PC 	5 /1		
4.	AXIAL T1- PRE CONTRAST	PER NORMAL CLINICAL SCAN		N.
5	AXIAI T1- POST CONTRAST	PER NORMAL CURICAL SCAN		•

MRI Technician	

NF Database ID#	Date of Scan
NF Study#	

NF1 ACQUISITION PROTOCOL

MRI PROTOCOL-TRUNK/EXTREMITIES

NOTE: ALL SERIES WITH THE EXCEPTION OF # 1 AND #2 SHOULD BE PERFORMED PER A NORMAL CLINICAL SCAN AS SPECIFIED BY THE RADIOLOGIST. THESE ADDITIONAL SERIES #1 AND #2 MAY OR MAY NOT BE PART OF THE NORMAL CLINICAL SCAN SEQUENCE, HOWEVER THESE SERIES ARE REQUIRED FOR THE NF1 STUDY PROTOCOL AND MUST BE PERFORMED WITHIN PROTOCOL SPECIFICATIONS AS INDICATED BELOW.

1.	AXIAL PLANE-STIR	Protocol Specifications	Actual Specifications	Reason For Change			
	COIL: BODY	_	-				
	SEQUENCE: FAST SPIN ECHO (TURBO) FSEIR						
	 ECHO TRAIN LENGTH: 8 						
	• TR	6000					
	• TE	15					
	• TI	150					
	 SLICE THICKNESS 	10 MM					
	■ SKIP	0					
	 MATRIX 	512x160					
	FOV	40 X 30					
	 Number of excitations/sequence 	0.5					
	 Number of acquistions 	1					
	 SATURATION 	NONE	*****				
2.	CORONAL PLANE - STIR						
۷.	COIL: BODY						
	SEQUENCE: FAST SPIN ECHO (TURBO) FSEIR						
	Echo Train Length: 12	TOLIK					
	• TR	3400					
	• TE	15		····			
	• TI	150					
	SLICE THICKNESS	5 MM					
	■ SKIP	0					
	MATRIX	512 X 160					
	FOV	48 x 48					
	NUMBER OF EXCITATIONS/SEQUENCE	1					
	Number of acquistions	î					
	SATURATION	NONE					

MRI	Tec	chnician	

NF Database ID#	Date of Scan
NF Study#	

NF1 ACQUISITION PROTOCOL

MRI PROTOCOL- SPINE

NOTE: ALL SERIES WITH THE EXCEPTION OF # 4 AND #5 SHOULD BE PERFORMED PER A NORMAL CLINICAL SCAN AS SPECIFIED BY THE RADIOLOGIST. THESE ADDITIONAL SERIES #4 AND #5 MAY OR MAY NOT BE PART OF THE NORMAL CLINICAL SCAN SEQUENCE, HOWEVER THESE SERIES ARE REQUIRED FOR THE NF1 STUDY PROTOCOL AND MUST BE PERFORMED WITHIN PROTOCOL SPECIFICATIONS AS INDICATED BELOW.

1	CACETTAL T1	I OCALIZED CODIE COIL
1.	SAGILIAL LI	LOCALIZER—SPINE COIL

2. SAGITTAL T1

3. SAGITTAL FSEIR

PER NORMAL CLINICAL SCAN PER NORMAL CLINICAL SCAN PER NORMAL CLINICAL SCAN

4.	AXIAL FSEIR	Protocol Specifications	Actual Specifications	Reason For Change
	 ECHO TRAIN LENGTH: 8 		•	
	TR	6000		
	• TE	34		***
	• TI	150		
	 SLICE THICKNESS 	5 MM		
	 SKIP 	0		
	 MATRIX 	256 x 256		
	FOV	22 CM		
	■ NEX	1		
	 Frequency Direction 	R→L		
	• OPTIONS: TAILORED RF, FC, PC, 0.	75 FOV		
5.	CORONAL FSEIR			
	■ ECHO TRAIN LENGTH: 8			
	TR	6000		
	• TE	34		
	• TI	150		
	 SLICE THICKNESS 	5 MM		
	 SKIP 	1 MM		
	 MATRIX 	256 x 256		
	• FOV	22 CM		
	• NEX	1		
	Frequency Direction	S→I		

6.	AXIAL T1	PER NORMAL CLINICAL SCA
7	AYIAI T1- POST CONTRAST	PER NORMAL CLINICAL SCA

OPTIONS: TAILORED RF, FC, PC

Appendix N

NF Patient ID#		
NF Fauent 1D#		

Date of Visit	
---------------	--

Natural History of Plexiform Neurofibromas in NF1

_						
	CONFIRMATION FAX					
`o:			From:	Brian Giglio		
ite:			WorldCare Fax::	(617) 374-9991		
ite Fax:			WorldCare Phone:	(617) 250-5174		
ite Phon	ie:		Re:	NF1 Fax Confirmation to Site		
	□ Urgent	☐ For Review	☐ Please Comment	□ Please Reply		
	Date World	Care received NF1 Data	Collection Form:	.//		
	Date MRI is	mages received:				
	Materials co	ompleted (Y/N):				
	Material ac	ceptable (Y/N):				
	Additional	Comments:				

Appendix O

FILE TRANSFER PROTOCOL PROCEDURE

COLLECTION CENTERS Children's Hospital

STEP 1

PATIENT AND PATIENT ID ASSIGNMENT NOTIFICATION OF POTENTIAL

- 1. PCC will provide BCH with eligibility forms of potential patient.
- 4. BCH will notify WC by fax Coordinator will provide 3. Via email PCC Clinical performed to BCH.

:

1. WC will review incoming

data set for compliance

with NF1 Acquisition

AND CONFIRMATION

DATA OA /OC

STEP 3

confirmation fax to both

PCC and BCH.

2. WC will fax study

Protocol.

will proceed to next step.

4. If study deemed

3. If data set accepted WC

- If eligibility approved, BCH
 - Number and notify the PCC. the date patient scan will be will assign patient ID
- of new patient, ID no., and the date of scan.

► STEP 4 YES acquired properly? S Z COLLECTION STEP 2 CENTERS Was study Children's Hospital SC £ 1 WorldCare SC

conjunction with BCH will

unacceptable WC in

STEP 2 will be repeated.

request re-scan and

DATA ANALYSIS AND ARCHIVAL @ WC

- Through FTP, WC will and convert all data to translation station and receive data to a data
- 2. Standardized data will be imported to a qualitative image review station. a standard format.
- analysis. After radiologist perform 3D Volumetric review, WC will record 3. WC technician will these results on the
- BCH and WC will maintain a copy of all data on file. 4. The original MRI DF will be forwarded to MRI DF.

DATA COLLECTION STEP 2

copies of AP and DCF are to be filled @ PCC

perform additional scans normal clinical scan and per the NF1 acquisition

Transfer of Images

ACCUISITION PROTOCOL

FTP

COLLECTION CENTERS

- Protocol form, and DCF. Fax completed originals complete Acquisition
- will forward these forms to AP and DCF forms, BCH FTP procedures.

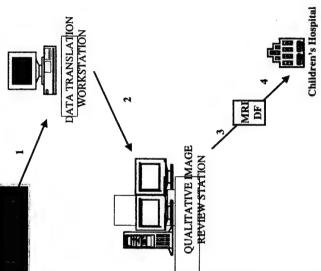
SC

Children's Hospital

WC using the appropriate

ROTOCOL

2



AND DATA TRANSFER

- 1. PCC will scan patient per protocol.
 - 3. Transfer patient images to 2. PCC technician will containing to BCH.
- WC within one business day 4. Upon receipt of the faxed of receipt.

Appendix P

Billing Period: 4/1/99-6/30/99 Invoice Date: 7/1/99
Period: 1

Patient Visit Reimbursement Form

Natural History of Plexiform Neurofibromas in NF1

Please Note:

- As stated in the protocol, patients should be seen approximately every 6 months.
- Reimbursement is NOT contingent upon MRI scans.

Date of Visit	*Patient ID#
Total Patient Contacts:	

^{*}Please use patient ID# assigned by Children's Hospital on the patient registration form

PAYABLE TO:

Washington University

MAILING ADDRESS:

Mary Corcoran, Assistant Controller Washington University 7425 Forsyth Clayton, MO 63105-2103

Return this form to:

Angela Doran Research Finance Children's Hospital Longwood Avenue Boston, MA 02115

Attachment B



HEADQUARTERS, U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND (USAMRMC)

Facsimile Transmittal Header Sheet FAX #: DSN 343-7803, (301) 619-7 Number of pages including this page =

From:

USAMRMC, DCSRCQ

504 Scott Street

Fort Detrick, MD 21702-5012

Office

MCMR-RCQ-HR

Symbol:

Office of the Deputy Chief of Staff for Regulatory Compliance and Quality

DSN 343-7486 Phone #:

(301) 619-7486

Internet: Sonya.Lewis@det.amedd.army.mil

Point of

Contact:

Sonya Lewis

To: Ms. Mary Sanford

Date: 30 September 1999

Dear Ms. Sanford:

I am sending you a list containing the various sites that have received conditional approval and final approval from the United States Army. Please note that this list comprises ten sites. Approval for Australia's consent form is pending. Considering that their Ethics Committee did not approve of the collection of blood for this study, the protocol must be amended to reflect this. Please speak with Dr. Korf regarding this issue. If additional institutions are to be included in this study, please supply me with their respective consent forms.

Sincerely,

Sonya Lewis, MS

Sougaseurs

Human Subjects Protection Specialist

Γ					_			66/			٦
Conditional approval letters sent out to:	Children's Memorial Hospital, Chicago 07/08/99	Baylor College of Medicine, Texas 07/16/99	University of British Columbia 08/31/99	Children's Hospital Med. Ctr., Cincinnati 09/16/99	Washington University Medical Center 07/16/99	Final approval letters sent out to:	Children's Hospital, Boston 06/14/99	Children's National Medical Center, Wash. DC 06/14/99	Children's Hospital Oklahoma 09/21/99	Guy's Hospital, London 09/22/99	
A-8394 Dr. Korf: MULTIPLE SITE NF1 STUDY Conditional approval letters sent out to:											
A-8394											

Attachment C

Neurofibroma Tumor Repository Progress Report

David H. Gutmann, MD-PhD Mark Watson, MD-PhD

The Neurofibroma Tumor Repository (NTR) provides a valuable resource for ongoing as well as future studies aimed at investigating the molecular pathogenesis of NF1 plexiform neurofibromas. Over the past 12 months, we have developed the NTR infrastructure for the collection of tumor specimens as well as white blood cells. Instead of extracting DNA, RNA and protein from the blood samples received from each patient, we have instead opted to freeze white blood cells in cryopreservative. This will allow us to immortalize these leukocytes in the future when it might be necessary to procure DNA, RNA and protein. We chose this approach, as it will provide a renewable source of material. In addition, we can obtain 300 specimens from all patients enrolled in this study for future genotype-phenotype correlations. To date (9-10-99), we have received 10 blood specimens from participating clinical centers. No plexiform neurofibroma specimens have been received thus far.

Since active enrollment only commenced in June 1999, we are anticipating a large volume of specimens over the next 12 months. No problems with tissue handling have occurred and the infrastructure appears sound and highly functional.

Attachment D



Department of Pathology

October 21, 1999

Bruce R. Korf, M.D., Ph.D. Partners Center for Human Genetics Harvard Institutes of Medicine Building 77 Avenue Louis Pasteur, Suite 642 Boston, MA 02115

Dear Dr. Korf:

I'm writing you to officially confirm my willingness to serve as the head of the pathology core for your grant entitled "Natural History of Plexiform Neurofibromas in NF1". As such, I will make our clinical and research facilities available for the diagnostic and investigative work-up of tissue specimens obtained from patients in your study. I look forward to working with you and other members of your team. I am confident that our collaboration will be productive. Thank you for the opportunity to participate.

Division of Neuropathology

Robert E. Schmidt, M.D., Ph.D. Richard M. Torack, M.D. Kevin A. Roth, M.D., Ph.D.

Arie Perry, M.D.

John C. Morris, M.D. Alan Pestronk, M.D.

Sincerely,

Arie Perry, M.D.

Assistant Professor of Pathology Division of Neuropathology

AP:als

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2. Photocopy this page or follow this format for each person.

NAME

Perry, Arie

POSITION TITLE

Assistant Professor of Pathology

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
The University of Texas at Austin, TX The U. of Texas Southwestern Med. School, Dallas, TX	B.S.	1986	Zoology
	M.D.	1990	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publication in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES. PROFESSIONAL EXPERIENCE:**

I INOX EDDIOTIVE	BIM BIMBITOR
1988	Autopsy Externship, Department of Pathology, Univ. of Texas Southwestern Medical School
1990-1994	Pathology Residency (AP/CP), Parkland Memorial Hospital, Univ. of Texas Southwestern Medical
	School
1994-1995	Surgical Pathology Fellowship, Mayo Clinic; Rochester, MN
1995-1998	Neuropathology and Research Fellowships, Mayo Clinic; Rochester, MN
1998-Present	Assistant Professor, Department of Pathology; Washington Univ. School of Medicine; St. Louis, MO

HON	ORS:
-----	------

1993	First place resident poster presentation award, Texas Society of Pathologists
1994	First place resident podium presentation award, Texas Society of Pathologists
1994	Matthew T. Moore travel fellowship award, International Congress of Neuropathology
1995	Mary Tom Award, Canadian Association of Neuropathologists
1995-1997	American Brain Tumor Association Fellowship Award
1999	Distinguished Service Teaching Award, Washington University School of Medicine, Medical
	School Class of 2001

PUBLICATIONS:

- Perry A, Hernandez JA: Double heterozygous hemoglobin E/Beta thalassema. ASCP Check Path. Case QAH 92-4, 1992; J162.
- Perry A, Duenzl ML, Ansari MQ: Flow cytometric terminal deoxynucleotidyltransferase analysis. Evaluation of triton-X-100 and methanol permeabilization methods compared with immunofluorescence microscopy. Arch. Pathol. Lab. Med. 1994; 118:1119-1122.
- Wiley EL, Perry A, Nightingale SD, Lawrence J: Detection of mycobacterium avium-intracellulare complex in bone marrow specimens of patients with acquired immunodeficiency syndrome. Am. J. Clin. Pathol. 1994; 101:446-451.
- Perry A, Wiley EL, Albores-Saavedra J: Pagetoid spread of intratubular germ cell neoplasia into rete testis: A morphologic and histochemical study of 100 orchiectomy specimens with invasive germ cell tumors. Hum. Pathol. 1994; 25:235-239.
- Perry A, Vuitch F: Causes of death in patients with sarcoidosis. Arch. Pathol. Lab. Med. 1995; 119:167-172. Perry A, Molberg K, Albores-Saavedra J: Physiologic vs. neoplastic C-cell hyperplasia: separation of distinct

histologic and biologic entities. Cancer 1996; 77:750-756.

Perry A, Jenkins RB, Dahl RJ, Moertel CA, Scheithauer BW: Cytogenetic analysis of aggressive meningiomas. Possible diagnostic and prognostic implications. Cancer 1996; 77:2567-2573.

- Giannini C, Scheithauer BW, Jenkins RB, Erlandson RA, Perry A, Borell TJ, Hoda RS, Woodruff JM: Soft-tissue perineurioma. Evidence for an abnormality of chromosome 22, criteria for diagnosis, and review of the literature. Am. J. Surg. Pathol. 1997; 21:14-173.
- Perry A, Giannini C, Scheithauer BW, Rojiani AM, Yachnis AT, Seo IS, Johnson P, Kho J, Shapiro S: Composite pleomorphic xanthoastrocytoma and ganglioglioma: report of four cases and review of the literature. Am. J. Surg. Pathol. 1997; 21:763-771.
- Perry A, Tonk V, McIntire D, White C: Interphase cytogenetic (in situ hybridization) analysis of astrocytomas using archival formalin-fixed, paraffin-embedded tissue and light microscopy. Am. J. Clin. Pathol. 1997; 108:166-174.
- Perry A, Parisi JE, Kurtin PJ: Metastatic adenocarcinoma to the brain: an immunohistochemical analysis. Hum. Pathol. 1997; 28:938-943.

PHS 398 (Rev. 5/95)

(Form Page 6) Page

FF

- Perry A, Nobori T, Ru N, Anderl K, Borell TJ, Mohapatra G, Feuerstein BG, Jenkins RB, Carson DA: Detection of p16 gene deletions in gliomas: Fluorescence *in situ* hybridization (FISH) versus quantitative PCR. J. Neuropathol. Exp. Neurol. 1997; 56:999-1008.
- Perry A, Scheithauer BW, Nascimento AG: The immunophenotype of meningeal hemangiopericytoma: a comparison with fibrous meningioma and solitary fibrous tumor of meninges. Am. J. Surg. Pathol. 1997; 21:1354-1360.
- Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM: Meningioma grading: an analysis of histologic parameters. Am. J. Pathol. 1997; 21:1455-1465.
- Stafford SL, Perry A, Leavitt JA, Garrity JA, Suman V, Scheithauer BW, Meyer FB: Anterior visual pathway meningiomas primarily resected between 1978-88. The Mayo Clinic experience. J. Clin. Neuro-Opthalmol. 1998; 18:206-210.
- Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM: The prognostic role of MIB-1, p53, and DNA flow cytometry in completely resected primary meningiomas. Cancer. 1998; 82:2262-2269.
- Stafford SL, Perry A, Suman VJ, Meyer FB, Scheithauer BW, Lohse CM, Shaw EG: Primarily resected meningiomas: Outcome and prognostic factors in 581 Mayo Clinic patients, 1978-1988. Mayo Clinic Proc. 1998; 73:936-942.
- Perry A, Scheithauer BW, Stafford SL, Abell-Aleff PC, Meyer FB: "Rhabdoid" meningioma: an aggressive variant. Am. J. Surg. Pathol. 1998; 22:1482-1490.
- Perry A, Scheithauer BW: Malignant transformation of meningioma: an example with rhabdoid morphology with a discussion of meningioma grading. Pathol. Case Rev. 1998; 3:296-300.
- Perry A, Scheithauer BW, Zaias BW, Minassian HV: Aggressive enterogenous cyst: report of a case with extensive craniospinal spread. Neurosurgery 1999; 44:401-405.
- Perry A, Stafford SL, Scheithauer BW, Lohse CM, Wollan PC: "Malignancy" in meningiomas: a clinicopathologic study of 116 patients. Cancer 1999; 85:2046-2056.
- Smith JS, Alderete B, Minn Y, Borell TJ, Perry A, Mohapatra G, Smith SM Kimmel D, Yates A, Feuerstein BG, Burger PC, Scheithauer BW, Jenkins RB: Localization of common deletion regions on 1p and 19q in human gliomas and their association with histological subtype. Oncogene 1999; 18:4144-4152.
- Perry A, Jenkins RB, O'Fallon JR, Mahoney MR, Scheithauer BW, Smith SM, Hill EM, Sebo TJ, Buckner JC: Clinicopathologic study of uniformly treated anaplastic astrocytomas: an analysis of DNA content (ploidy), cellular proliferation, and p53 expression. Cancer 1999; 86:672-683.
- Couce ME, Perry A, Webb P, Scheithauer BW: Fibrous meningioma with tyrosine-rich crystals. Ultrastructural Pathol. *In press*.
- Adlakha A, Rao K, Adlakha K, Perry A, Crotty TB, Scheithauer BW, Ryu JH. Metastatic meningioma to the lung. Mayo Clin. Proc. In press.
- Perry A, Anderl KA, Borell TJ, Kimmel DW, Wang CH, O'Fallon JR, Feuerstein BG, Scheithauer BW, Jenkins RB. Detection of p16, RB, CDK4, and p53 gene deletion / amplification by fluorescence in situ hybridization (FISH) in 96 gliomas. Am. J. Clin. Pathol. *In press*.
- Smith JS, Perry A (co-first author), Borell TJ, Lee HK, O'Fallon J, Smith SM, Kimmel D, Burger PC, Scheithauer BW, Jenkins RB. Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas. J. Clin. Oncol. *In press*.
- Raffel C, Frederick L, O'Fallon JR, Atherton-Skaff P, Perry A, Jenkins RB, James CD. Analysis of oncogene and tumor suppressor gene alterations in pediatric malignant astrocytomas reveals reduced survival for patients with PTEN mutations. Clin. Cancer Res. *In press*.
- Perry A, Scheithauer BW. Chapter 10: Neuropathology. In: Chang YW, Bostwick DG (ed.) Essentials of anatomic pathology. A practical guide with emphasis on differential diagnosis and diagnostic criteria. Seattle: United Pathologist Press In press.
- Perry A, Leonard JR, Roth KA, Gutmann DH. Tumor Genetics. In: Batjer HH, Loftus CM (ed.) Textbook of Neurological Surgery. Philadelphia: Lipincott Williams and Wilkins In press.
- Smith JS, Tachibana I, Lee HK, Qian J, Pohl U, Mohrenweiser HW, Borell TJ, Hosek SM, Soderberg CL, von Deimling A, Perry A, Scheithauer BW, Louis DN, Jenkins RB. Mapping of the chromosome 19 q-arm glioma tumor suppressor gene using fluorescence in situ hybridization (FISH). *Oncogene*

ABSTRACTS:

Bruch LA, Hill DA, Dehner LP, Perry A: A role for FISH detection of chromosome 22q dosage in distinguishing atypical teratoid/rhabdoid tumors from central PNET/medulloblastomas. Neuro-Oncology 301; 1999.

Attachment E

The Study of Natural History of Plexiform Neurofibromas in NF1

This is a research study of the rate of growth of plexiform neurofibromas. Plexiform neurofibromas are a particular type of benign tumor that occurs in persons with neurofibromatosis type 1. The growth patterns of these tumors appear to be unpredictable and the factors that influence that growth are largely unknown. The goal of this study is to closely monitor the growth of plexiform neurofibromas for a period of at least three years using magnetic resonance imaging (MRI). This technique will permit us to measure the overall size (volume) of the plexiform neurofibroma. By repeating the assessment every 6-24 months we hope to be able to document the rate of change in size of the plexiform neurofibroma.

This is an international study in which 300 individuals with NF1 will be enrolled. The study is being directed by Bruce R. Korf, M.D., Ph.D., Clinical Director of Genetics at Boston's Children's Hospital. Patients are being recruited at 18 different institutions worldwide (see list of center locations).

This study is sponsored by the US Army Medical Research Material Command (USAMRMC). To learn more about the USAMRMC go to: http://mrmc-www.army.mil/

Participation Objectives Entry/ Exclusion Criteria Center Locations Contact Us Links

Participation

What does participation in the study mean?

Participation in this study will involve both clinical assessment and MRI scanning. The clinical assessment will occur every six months for three years. A standard physical examination will be done, the same as for a standard clinic visit. If the plexiform neurofibroma is visible on the surface it will be measured with a ruler or tape measure and photographs will be taken. Since these visits are deemed part of your clinical care, they will be billed to your medical insurance as standard clinical visits. A clinic note will be placed in the medical record and copies sent to your primary care provider, as is standard in the clinic. Data about your clinical assessment will be entered into a computer database. This clinical data is also sent to a central database maintained by the University of British Columbia, sponsored by the National Neurofibromatosis Foundation. You will be identified in this central database only by a code number, but not by name, to preserve confidentiality. Photographs of your plexiform neurofibroma will be kept in a confidential file in the Division of Genetics. Clinic visits will occur over a period of 30-45 minutes.

At the time of the first clinic visit when this study begins a blood sample will be obtained from you. The blood sample will be drawn from a vein in the arm, and will consist of approximately 5-10 cc (1-2 teaspoons). This sample will be used as a source of DNA, the genetic material inside our cells. We will also obtain serum (the liquid component of blood). This DNA and serum will be sent to a central tissue repository at Washington University in St. Louis and banked there. There are no immediate plans to study this DNA and serum, but at some point in the future it may be possible to examine the DNA for the changes in the NF1 gene, or in other genes that may alter the behavior of neurofibromas. The serum may be used to test for substances in the blood that cause neurofibromas to grow. Since we will be monitoring the growth of the neurofibroma carefully, we hope to have the opportunity to examine genetic or serum factors that may influence tumor growth at some point in the future. There is no assurance, however, that such testing will be possible or necessarily will be done. Any results obtained from DNA or serum studies will be kept confidential. You will have the opportunity to designate whether you would like to learn the results of such testing in the future, and whether you would like us to share these results with any health providers whom you designate. You can direct us to withdraw the blood sample from the repository at any time.

MRI scanning of the plexiform neurofibroma will be part of this study. Every participant will have an MRI at the time of enrollment into the study (unless the plexiform neurofibroma has been followed by MRI for a period of time before the study and is known to have not changed in size). A second MRI will be done one year later unless there are clinical reasons to do it sooner. MRI will be repeated at the end of the study, at three years. If the neurofibroma appears to be growing, either based on clinical assessment or from measurements of the MRI scans, follow-up MRI may be done more often, at the discretion of your physician, in accordance with standard clinical care.

In most cases these MRI scans are used in standard clinical care and will therefore be billed to your insurance. There may be some instances in which an MRI might not have been performed for routine clinical purposes at the same time as designated by the study. In these cases, funds are available to defray the costs of the MRI scan. In some instances it will be necessary to use sedation or general anesthesia. Consent for this procedure will be obtained by the radiologist or anesthesiologist prior to the procedure. Also, in some cases, it will be necessary to insert an intravenous line and administer contrast material into the vein. This will be done at the discretion of the radiologist, if it appears that contrast is necessary to better visualize the neurofibroma. Your consent will be obtained prior to this procedure. We expect that the MRI scans will require approximately one hour.

We do not plan to perform surgery or take a sample of the plexiform neurofibroma as part of this study, but in some cases surgery may be performed because of clinical indications. This decision will not be influenced by your participation in the study, and will not affect your participation in the study. If there is neurofibroma tissue available that is not needed for examination as part of clinical care, this tissue will be collected and sent to a central tissue bank at Washington University in St. Louis. In addition, a sample will be sent to Mt. Sinai School of Medicine for review of the pathological features of the neurofibroma. The tissue will be identified with a code number, and will only be possible to connect with your name through our clinic. The tissue may be distributed to investigators to help with their research on neurofibromatosis. Any future research done with these samples will be conducted under a protocol approved by the Institutional Review Board with oversight of the tissue bank. It is not anticipated that results of study of your neurofibroma tissue will influence clinical management, and therefore you will not be informed of research results on this tissue. All research results will be kept confidential. You can withdraw your specimen from the tissue repository at any time.

Study Objectives

- A. Determine the efficacy of volumetric MRI for measurement of the growth rate of plexiform neurofibromas.
- B. Provide a body of normative data on the growth rate of plexiform neurofibromas. Although limited by a relatively short study period, the following hypotheses will be tested:
 - Most plexiform neurofibromas grow out of proportion with somatic growth for period of time during childhood but reach a plateau by the end of puberty;
 - Patterns of neurofibroma growth may vary from patient to patient but there are systematic differences in growth patterns according to location of the neurofibroma in the body;
- C. Establish a consortium of clinical centers supported by a tissue repository and central review of pathology, radiology, and statistical data.

Entry Criteria

- A. **Diagnosis of Neurofibromatosis:** All study subjects will fulfill diagnostic criteria for NF1.
- B. **Plexiform Neurofibroma:** A plexiform neurofibroma fulfilling entry criteria for the study will be defined as a diffuse soft tissue or nerve enlargement in a patient with NF1 that is causing or has potential to cause disfigurement or functional disability.
- C. **Distribution of Plexiform Neurofibromas by site:** A total of 300 plexiform neurofibromas will be studied, consisting of 100 tumors in the following three groups (based on region of maximal involvement):
 - 1. Head and Neck
 - 2. Trunk and Limbs (externally visible)
 - 3. Trunk and Limbs (internal)

Exclusion Criteria

- A. Presence of metallic implant that will make the patient unable to have MRI studies
- B. Presence of medical or psychological condition that will make the patient unable to tolerate MRI studies or anesthesia (if needed)
- C. Inability to image tumor or define tumor margins by MRI (which may be determined after the initial study)
- D. Failure to obtain initial MRI within 60 days of enrollment
- E. Previous radiation therapy to site of plexiform neurofibroma
- F. Surgery involving the plexiform neurofibroma (excluding biopsy) within a six month period before enrollment
- G. Current antineoplastic therapy

Center Locations and Physicians

Alan Rubenstein, M.D. Mt. Sinai School of Medicine 1 Gustave Levy Place New York, NY 10029

Bruce R. Korf, M.D., Ph.D. Children's Hospital 300 Longwood Ave. Boston, MA 02115

David Gutmann, M.D., Ph.D. Washington University School of Medicine 660 S. Euclid Ave. St. Louis, MO 63110

David Viskochil, M.D., Ph.D. University of Utah, School of Medicine Division of Medical Genetics 413 MREB 50 N. Medical Dr. Salt Lake City, UT 84112

Eric Legius, M.D. University of Leuven Kon Elisabethlaan 20 Leuven B-3000 Belgium

Fernando Kok, M.D. University of Sao Paulo de Grendo Juliete 233 04721060 Sao Paulo, Brazil

Jan Friedman, M.D., Ph.D. University of British Columbia 4500 Oak St. Vancouver, BC

Joel Charrow, M.D., Ph.D. Children's Memorial Hospital 2300 Children's Plaza Chicago, IL 60614

Locations

John J. Mulvihill, M.D. Children's Hospital of Oklahoma 940 NE 13th St., Room 2418 Oklahoma City, OK 73104

Kathryn North, M.D. Royal Alexandra Hospital PO Box 3515 Parramatta, NSW 2124 Australia

Mia MacCollin, M.D., Ph.D. Massachusetts General Hospital Bldg 149, 13th St., Boston, MA 02129

Robert Hopkins, M.D. Children's Hospital Medical Center 3333 Burnet Ave., Cincinnati, OH 45229-2899

Roger Packer, M.D. Children's National Medical Center 111 Michigan Ave. NW Washington, D.C. 20010

Rosalie Ferner, M.D. Guys Hospital St. Thomas' St. London, UK SE1 9RT

Sharon Plon, M.D., Ph.D. Texas Children's Hospital Division of Hematology-Oncology 6621 Fannin St., 3-3320 Houston, TX 77030

Susan Huson, M.D.
Oxford University
Department of Clinical Genetics
Churchill Hospital
Headington, Oxford, UK
0X3 7LJ

Victor-Felix Mautner, M.D. Klinikum Nord Ochsenzoll Langenhorner Chaussee 560

Locations

22419 Hamburg, Germany

Study Home Page Participation Objectives Entry/ Exclusion Criteria Contact Us Links

If you or your child would like to participate in the Study of Natural History of Plexiform Neurofibromas in NF1 or you would like

If you or your child would like to participate in the Study of Natural History of Plexiform Neurofibromas in NF1 or you would like further information please contact:

Mary Sanford Research Study Coordinator Children's Hospital Division of Genetics 300 Longwood Avenue Boston, MA 02115

Phone: (617) 355-3479 Fax: (617) 355-7588

Email: sanford_m@hub.tch.harvard.edu

CONTACT US: sanford_m@hub.tch.harvard.edu

Other Links

Neurofibromatosis Links

Link to the National Neurofibromatosis Foundation (NNFF) http://www.nf.org/

Link to the NIH National Institute of Neurological Disorders and Stroke http://www.ninds.nih.gov/HEALINFO/DISORDER/NEUROFIB/NEUROFIB.HTM

Link to the Massachusetts General Hospital NF Clinic home page http://neurosurgery.mgh.harvard.edu/NFclinic.htm

Link to the Neurofibromatosis Resources Webpage http://neurosurgery.mgh.harvard.edu/NFR/

Link to the University of Washington at Seattle Gene Clinic http://www.geneclinics.org/profiles/nf1/

Link to NF Inc. http://www.nfinc.org/

Link to The Neurofibromatosis Web. A place for people with NF to communicate with each other.

http://193.192.226.150:80/neurofibromatosis/

Link to the NF Inc. Links Page http://www.nfinc.org/links.html

If you would like to add a website to this list, please contact Mary Sanford at: sanford_m@hub.tch.harvard.edu

Attachment F



To: Mary Sanford

From: Brian Giglio

CC: Bruce Korf, Jay Zimmerman, Colette Lajeunesse

Date: 10/28/99

Re: Army Report for Natural History of Plexiform Neurofibromas in NF1

a) List of all centers that have submitted test data

The following MRI centers have submitted test data for the NF1 Study either by optical disk or through File Transfer Protocol (FTP):

 Children's Hospital Neurofibromatosis Program 300 Longwood Ave.
 Boston, MA 02115

2. Center for Human Genetics

University of Leuven Kon Eliaabethlaan 20 Leuven B-3000, Belgium

 Children's Hospital Medical Center Neurofibromatosis Center
 Burnet Ave.
 Cincinnati, OH 452229 - 2899

 Children's Memorial Hospital Neurofibromatosis Clinic
 Children's Plaza Chicago, IL 60614

 Children's Hospital of Oklahoma (CHO) Neurofibromatosis Program
 NE 13th St. Room 2418
 Oklahoma City, OK 73104

 Children's National Medical Center Neurofibromatosis Program
 Michigan Ave.
 Washington, D.C. 20010

7. Guys Hospital Neurofibromatosis Program St. Thomas' St. London, UK SE1 9RT 8. Klinikum Nord Ochsenzol Neurological Department Langenhomer Chausee 560 D-22419 Hamburg, Germany

 Massachusetts General Hospital Neurofibromatosis Clinic Building 149
 13th Street Charlestown, MA 02129

 Mount Sinai Medical Center Department of Neurology
 One Gustave L. Levy Place
 New York City, NY 10029-6574

 Royal Alexandria Hospital Neurofibromatosis Clinic
 PO Box 3515
 Parramatta, NSW
 Australia

12. Texas Children's Hospital Division Hematology - Oncology 6621 Fannin St., 3 - 3320 Houston, TX 77030

13. University of British ColumbiaRoom C2014500 Oak St.Vancouver, British Columbia V6T1Z3

14. University of UtahDivision of Medical Genetics413 MREB50 N. Medical Dr.Salt Lake City, UT 84112

15. Washington University Neurofibromatosis Program St. Louis Children's Hospital Box 8111 660S. Euclid Ave. St. Louis, MO 63110

Only one of these MRI centers, Guy's Hospital, has submitted a test data set that is not compatible with WorldCare's image viewing and measurement software. This issue is related to file corruption and another test data transfer is currently being addressed.

b) List of patient visits from each center

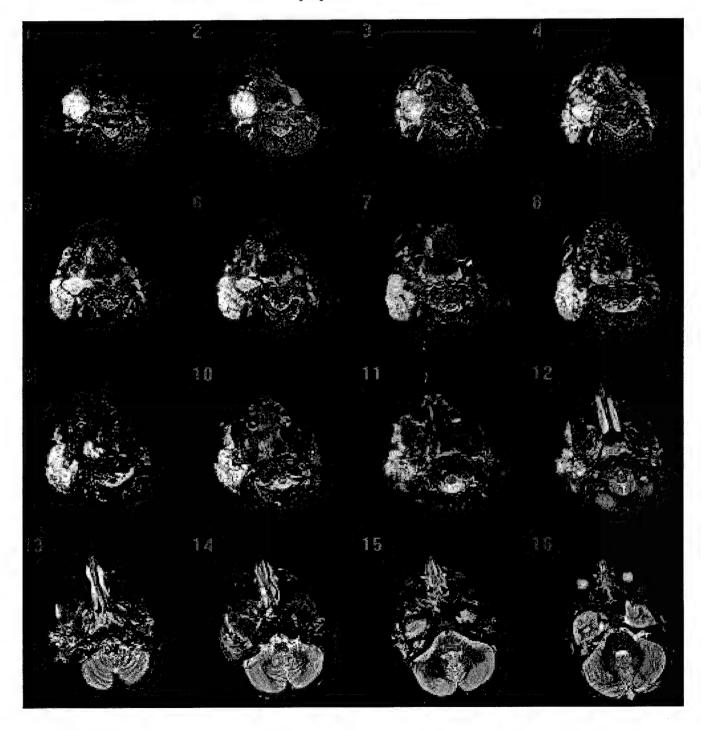
A total of twelve patient visits have been sent to WorldCare from two MRI centers to date. The following is a list of the patient visits received from each center:

Children's Hospital, Boston	Children's Hospital, Oklahoma
1. 107-0123-500	1. 178-0002-001
2. 107-0316-500	2. 178-0001-001

3. 107-0200-500	
4. 107-0632-500	
5. 100-0145-500	
6. 107-0160-500	
7. 107-0021-500	
8. 107-0055-402	
9. 107-0520-500	
10. 107-0524-500	

c) Example of volumetric data

The following is the image and measurement data resulting from volumetric analysis performed by a WorldCare technician on an NF1 sample patient:



• Page 3

The following spreadsheet tabulates the measurement results for each region of interest (ROI) in order to calculate the volume on the images displayed above for the NF1 sample patient:

IF1 Sample Patient									
						· · · · · · · · · · · · · · · · · · ·			
	Document	Mean	Max	Min	Std. Dev.	Area	Sum	Volume	
	f.des[1,1](RED)	807.97864	1383	73	269.03	1229.41	1,476,177.00	7376.476	
	f.des[2,1](RED)	766.94104	1338	83	279.91	1460.89	1,665,029.00	8765.369	
		743.37592	1379	119	221.15	1537.61	1,698,614.00	9225.642	
		737.92499	1054	309	177.13	53.8331	59,034.00	322.9984	
	f.des[3,1](RED)	594.90625	970	171	185.65	43.0665	38,074.00	258.3987	
	f.des[4,1](RED)	655.15625	1344	16	246.76	2652.62	2,582,626.00	15915.75	
		717.37024	1325	132	232.24	3004.56	3,203,058.00	18027.35	
		813.12482	1407	74	223.69	2194.37	2,651,600.00	13166.22	
	f.des[7,1](RED)		1608	184	242.60	1634.51	2,203,367.00	9807.04	
	f.des[8,1](RED)		1408	179	246.10	1873.39	2,352,383.00	11240.35	
		839.02924	1466	134	259.88	1979.71	2,468,424.00	11878.27	
y	f.des[10,1](RED)	857.86762	1459	163	247.93	1849.84	2,358,278.00	11099.03	
	f.des[11,1](RED)		1525	141	256.24	1701.13	2,027,936.00	10206.75	
	f.des[12,1](RED)		1528	93	274.76	1526.84	1,527,430.00	9161.043	
	f.des[13,1](RED)		1222	19	190.20	1866.66	1,212,123.00	11199.97	
· ····································	f.des[14,1](RED)		1238	0	191.52	1476.37	907,549.00	8858.232	
	f.des[15,1](RED)		1348	40	177.97	538.331	360,050.00	3229.984	
							Volume=	159.74	CM ³

d) Description of WorldCare's efforts in establishing the infrastructure and data analysis WorldCare has contributed to the NF1 Natural History Study infrastructure by preparing the WorldCare site for data collection and analysis and preparing the MRI centers for data collection and transfer. A private suite for the NF1 Natural History Study was prepared at WorldCare, Inc and houses hardware and software for sending and receiving images for the collection and analysis of patient data, including optical drives and translators. Also, a filing system, logbooks, and patient tracking database have been established to accept and track the workflow of patient data.

Standard operating procedure manuals were completed for both the WorldCare measurement center and the MRI centers. These manuals outline procedures for the collection, receiving and analysis of data specific to the study within Good Clinical Practices (GCP) guidelines. The MRI center SOP was merged with the NF1 Study Manual and has been distributed to the clinical coordinators at each MRI facility in the study. The WorldCare Measurement Center SOP has been entered into WorldCare Document Control and will be revised on as needed basis.

To date, WorldCare has qualified fifteen MRI facilities for the study. Each facility was required to complete a site survey detailing both MRI scanner and network hardware and software specifications. If these specifications fulfilled study guidelines, WorldCare requested a test data set to be sent either via FTP or on optical disk. A review of this test data ensured that the facilities' images and their method of data transfer were compatible with WorldCare's image viewing and analysis systems.

Both qualitative and quantitative analyses have been performed on ten enrolled patients. These patients were scanned and collected within the study protocol parameters. The images were collected and measured by a WorldCare Measurement Center Technician providing volumetric measurements of the plexiform neurofibromas. A sub-specialist radiologist will review these

measurements, and the finalized measurement results of the volumetric analysis will be recorded and forwarded to the NF1 Research Coordinator.

A radiologist review meeting is scheduled for November 1, 1999. Children's Hospital NF1 radiologists will review the first data sets measured by WorldCare technicians. This meeting will also be used to establish parameters for a validation study. This study will require WorldCare technicians and NF1 radiologists to perform volumetric analysis on the same patients. A Children's Hospital statistician will analyze these results to determine the variability between readers for volumetric analysis of NF1 plexiform neurofibromas. This study will be completed by January 1, 2000 providing the first publication of the NF1 study.

Attachment G

P.O#:

Ship To:

WorldCare



CLINICAL TRIAL DIVISION

WORLDCARE, INC.

One Cambridge Center Cambridge, MA 02142 Phone: (617) 374-9001 Fax: (617) 374-9991

Invoice

Bill To:

Dr. Bruce Korf Children's Hospital 300 Longwood Ave.

Boston, MA 02115

Invoice

Number

1722

Date Shipped:

Invoice

Date:

11/17/98

Item Description	Serial #	Price			
Import Workstation with high resolution m	onitor	\$2,625.00			
Dual Headed Analysis and Review Works	tation	\$4,750.00			
Pioneer Optical Drive		\$1,350.00			
Network Equipment		\$200.00			
2 Copies MEDStudio Pro Analysis Softwa	re	\$7,500.00			
1 Copy GE/SIEMENS Optical Reader		\$5,000.00			
4 year service contract for machines at WC	,	\$4,000.00			

Shipping & Handling:

NA

Terms: Net 30 Days

Make checks payable to: WorldCare, Inc.

Total:

\$25,425.00

NF1 / NF2 Equipment

Import Workstation

450 MHz Pentium II Processor 128 Meg. SDRAM Keyboard, Intellimouse 40X CDROM 16 MB STB mVidia AGP Video Card 1.44 MB Floppy

16.8 Gig Hard Drive McAfee Virus Scan Microsoft Windows 98 3COM 3C905B 10/100 PCI NIC 21" Hitachi Superscan 814 Monitor

Dual Headed Analysis and Review Workstation

450 MHz Pentium II Processor 256 Meg. SDRAM Keyboard, Intellimouse 40X CDROM Appian JeronimoPro 16 MB Video Card 1.44 MB Floppy 16.8 Gig Hard Drive
McAfee Virus Scan
Microsoft Window NT
3COM 3C905B 10/100 PCI NIC
(2) 21" Hitachi Superscan 814 Monitors
HPLaserjet Printer

Pioneer Optical Drive

Pioneer Optical Drive for reading Pioneer 502 and 702 opticals from scanners

Network Equipment

10/100 5 port HUB with uplink and Cat 5 cables

MEDStudio Pro Analysis Software

Software to perform the data review and analysis for 2D and 3D measurements

GE/SIEMENS Optical Reader

Software to retrieve and convert images stored on the proprietary GE and SIEMENS formatted optical disks (Pioneer 502/702) to DICOM 3.0 files.

3 or 4-year service contract for machines at WC

Full support for all hardware and software used in this trial including regular preventative maintenance.

Attachment H

			Billed																														
		MRI Data																															
		MDI Doto	Received by WC																														
	1#1		MRI Date		7/27/99																												
	Visit #1	04040	Received																														
hild			Received	8/23/99																													
Group A Head and Neck - Child		ata	Received	8/23/99																													
Gro		5	Enrolled	6/11/99	7/23/99	8/11/99	8/11/99	8/11/99	8/11/99	8/23/99	10/21/99																						
Head			Institution	CNMC	HO	НЭ	НЭ	HO	HO	CH	CHO																						
			Physician	Packer	Korf	Korf	Korf	Korf	Korf	Korf	Mulvihill																						
			Database ID#	170-0001-001	107-0200-500	107-0524-500	107-0521-500	107-0033-500	107-0032-500	107-0050-500	178-0001-001																						
			Study ID#	A01	A02	A03	A04	A05	A06	A07	A08	A09	A10	A11	A12	A13	A14	A15	A16	A17	A18	A19	A20	A21	A22	A23	A24	A25	A26	A27	A28	A29	A30

#	Database ID#	Physician	Heac	d and Neck Core Date Forms Enrolled Receiv	- Cata	pa	Visit #1	#1 MRI Date	Visit #1 Photos MRI Data Confirm Received MRI Date Received by WC	ata	Billed
A35 A36 A37 A37 A38											
A40 A41 A42 A43 A44											
A45 A46 A47 A48 A49 A50											

Group B Head and Neck - Adult	Visit #1	Core Data Forms	Physician Institution Enrolled Received Received MRI Date Received d by WC		Ferner GH 10/21/99		Ferner GH 10/21/99	Ferner GH 10/21/99																									
Hea			Physician	107-0261-500 Korf	Ferner	Ferner			B06	B07	B08	B09	B10	B11	B12	B13	B14	B15	B16	B17	B18	B19	B20	B21	B22	B23	B24	B25	56	B27	B28	29	- 06

		Г		Т	Т	Т		Г		Г		T				_	Γ.						Г
		D.	Billed																				
			MRI Data Confirme Received d by WC																				
		t #1	MRI Date																				
		Visit #1	Photos Received																				
	dult		Data MRI Data MRI Data Confirme Received MRI Data Confirme Received Data Data																				
lp B	Head and Neck - Adult		Core Data Data Forms Form Received Rece																				
Group B	and N		Date Enrolled																				
	Head		Institution																				
			Physician																				
			Database ID#																				
			Study ID#	B31	B32	B33	B34	B35	B36	B37	B38	B39	B40	B41	B42	B43	B44	B45	B46	B47	B48	B49	B50

			eq																														
		_ 7	Billed	_								_			L	_	_												_				
		MRI Data	by WC																														
		MRI Data	Received by WC																														
P	t #1				7/16/99		8/22/89						8/19/99																				
) - Chi	Visit #1	Dhotoe	Received Received MRI Date																														
Visible		Data	Received			8/23/99																											
Group C d Limbs (Externally Visible) - Child		Core Data	Received			8/23/99																											
Group C		Date	led	10/21/99	7/22/99	8/2/89	8/11/89	8/11/99	8/11/89	8/11/89	8/11/99	8/23/89	8/23/99	10/21/99	10/21/99	10/21/99	10/21/99																
			Institution	CNMC	K	CNMC	CH	H5	GH	CHO	CHO																						
Trunkan			Physician	Packer	Korf	Packer	Korf	Ferner	Ferner	Mulvihill	Mulvihill																						
,			Database ID#	170-0000-000	107-0520-500	170-0006-006	107-0160-500	107-0491-500	107-0632-500	107-0618-500	107-0021-500	107-0017-500	107-0123-500	168-003-0001	168-018-0001	178-0003-002	178-0004-001																
			Study ID#	C01	C02	C03	C04	C05	900	C07	C08	600	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28	C29	C30

				70																				
				Billed																				
			MRI Data	MRI Data Confirmed Received by WC																				
				Forms Photos MRI Date MRI Data Confirn Received MRI Date Received by WC																				
	p	t #1		MRI Date																				
) - Chi	Visit #1		Photos Received																				
	Visible		Data	Forms Received																				
Group C	d Limbs (Externally Visible) - Child		ata	Forms Received																				
Gro	s (Ext			Date Enrolled																				
	and Limk			Institution																				
	Trunk and			Physician				,																
				Database ID#														-						
				Stridy [D#	C31	C32	C33	C34	C35	C36	C37	C38	C33	C40	C41	C42	C43	C44	C45	C46	C47	C48	C49	C20

Group D	unk and Limbs (Externally Visible) - Adult	Visit #1	Core Data Data MRI Data	Date Forms Forms Photos MRI Data Confirmed Forms Received MRI Date Received Billed	CNMC 6/18/99 8/23/99	MC 6/24/99 8/23/99	Н 8/10/99	CH 8/23/99	CH 9/8/99 10/21/99 10/21/99	GH 10/21/99	GH 10/21/99		GH 10/21/99		GH 10/21/99	GH 10/21/99	GH 10/21/99	GH 10/21/99	GH 10/21/99 10/21/99	GH 10/21/99	GH 10/21/99	CHO 10/21/99										
	Trunk and Limbs			i	CNMC	CNMC			Korf CH			В		ВH			В				GH											
				Ct. do In the Contract of the			D03 107-0316-500	D04 107-0020-503	D05 107-0130-500	D06 168-0006-001	D07 168-0004-001	D08 168-0009-001	168-0010-001	D10 168-0011-001	D11 168-0012-001	D13 168-0001-001	D15 168-0014-001		D17 168-0016-001	D18 168-0019-001	D19 168-0020-001	D20 178-0003-001	D21	D22	D23	D24	D25	D26	D27	D28	D29	

					_		_		_	_			_	_					_					
				Billed																				
			MRI Data Confirmed	by WC																				
			MRI Data Confirmed	Received Received MRI Date Received by WC																				
	ult	t #1		MRI Date																				
	e) - Adı	Visit #1	Photos	Received																				
	Visible		Data Forms	Received																				
Q dr	Limbs (Externally Visible) - Adult		Core Data Forms	Received															:					
Group D	s (Exte		Date	Enrolled																				
				Institution																				
	Trunk and			Physician																				
				Database ID#																				
				Study ID#	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40	D41	D42	D43	D44	D45	D46	D47	D48	D49	D20

•

	Т			_	Т	Т	Г	Г	Г		Г	Г	Т					Г	Т		Г		Г	Г	Т	Г	<u> </u>	Г				
				Billed																												
			ıta ned																	,												
			MRI Data	Received by WC																												
	7.3	Visit #1		MRI Date											-																	
Pild		Visi	Photos	Received Received MRI Date																												
) - (le) - (IB)		Data Forms	Received 8/23/99	0000																											
Group E	וובוו		_	Received 8/23/99																												
Gro				Enrolled 6/23/99	10/21/99																											
Trimb and	ומוצ שוומ			Institution	CHO																											
F				Physician Packer	Mulvihill																											
				Database ID# 170-0003-003	178-0002-001																											
-				Study ID#	E02	E03	E04	E05	E06	E07	E08	E09	E10	E11	E12	E13	E14	E15	E16	E17	E18	E19	E20	E21	E22	E23	E24	E25	E26	E27	E28	E29

						Billed																				
				MRI Data	MRI Data Confirmed	by WC																				
					MRI Data	Received Received MRI Date Received by WC																				
			Visit #1			MRI Date																				
		hild	Vis		Photos	Received																				
	-	ıal) - C			Forms	Received																				
	Group E	k and Limbs (Internal) - Child		Core Data	Forms	Received																				
	Gro	Limbs				Enrolled																				
		Trunk and				Institution																				
						Physician																				
						Database ID#																				
E30						Study ID#	E31	E32	E33	E34	E35	E36	E37	E38	E39	E40	E41	E42	E43	E44	E45	E46	E47	E48	E49	E50

													Г	Г																			
				Billed																													
			MRI Data Confirmed																														
			MRI Data	Received Received MRI Date Received by WC																													
		Visit #1		MRI Date		1/11/99																											
	dult	Visi	Photos	Received																													
	al) - A		Data Forms	Received	8/23/89																												
Group F	k and Limbs (Internal) - Adult		Core Data Forms	þ	8/23/88																												
Gro	Limbs		Date	led	66/07/2	2/23/99																											
	Trunk and			_		CH																					11 6500						
				Physician	Packer	Korf																											
				Database ID#	170-0005-005	107-0055-402																											
				Study ID#	F01	F02	F03	F04	F05	F06	F07	F08	F09	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27	F28	F29

П					_														\neg						٦	
				4		Billed																				
				MRI Data	ned																					
					MRI Data	Received Received MRI Date Received by WC																				
			Visit #1			MRI Date																				
	1	dult	Vis		Photos	Received				,																
		ial) - A		_	Forms	Received																				
	np F	k and Limbs (Internal) - Adult		Core Data		Received																				
	Group F	Limbs				Enrolled																				
		Trunk and				Institution																				
						Physician																				
						Database ID#																				
F30						Study ID#	F31	F32	F33	F34	F35	F36	F37	F38	F39	F40	F41	F42	F43	F44	F45	F46	F47	F48	F49	F50

Attachment I

ANNOUNCEMENT

We will be holding a meeting on the subject of Clinical Trials in Neurofibromastosis Type 1 and the **Study of Natural History of Plexiform Neurofibromas in NF1**.

Friday July 16, 1999 12:00 - 3:00 PM

Children's Hospital Enders Auditorium 320 Longwood Ave Boston, MA 02115

The purpose of this meeting is to provide an update on clinical trials in NF1 and to describe the new study on the natural history of plexiform neurofibromas in NF1.

For more information please contact
Mary Sanford, Study Coordinator at (617) 355-3479 or
sanford_m@hub.tch.harvard.edu

Speakers will be **Bruce Korf, M.D., Ph.D.** and **Gretchen Schneider, M.S.**, Coordinator of the Neurofibromatosis Program.

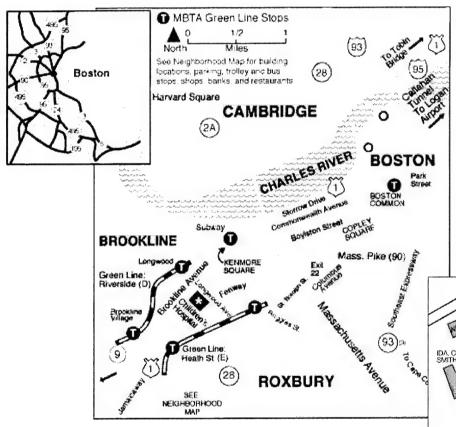
NF Clinic Children's Hospital Fegan 10

Fegan 10 300 Longwood Avenue Boston, MA 02115



Children's Hospital

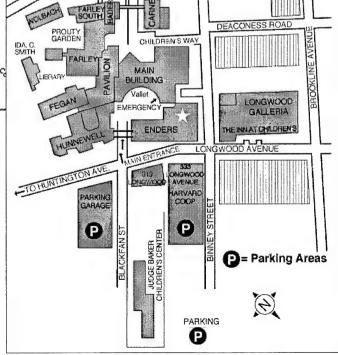
RETURN SERVICE REQUESTED



Parking is available at the Children's Hospital Parking Garage on the corner of Longwood Ave and Blackfan St.

For detailed directions visit the Children's Hospital Website

www.childrenshospital.org



Attachment J

NATURAL HISTORY OF PLEXIFORM NEUROFIBROMAS IN NF-1

This meeting is funded by the U.S. Army Medical Research with additional support from the National Neurofibromatosis Foundation

The Banbury Center, Cold Spring Harbor Laboratory, 6-9 February 1999

PROGRAM

Saturday, 6 February			
Afternoon	Amirrol at Dahartaan Hayaa	Donbury Conton	f

Afternoon	Arrival at Robertson House, Banbury Center, for registration and room assignment
6:00 pm	Reception at Robertson House

7:30 pm	Dinner a	at Robertson	House
---------	----------	--------------	-------

Sunday,	7	February
---------	---	----------

8:30-12:30	pm	SESSION I	:
------------	----	-----------	---

8:30-8:50 am Bri	ruce R. Korf, Children	s Hospital, Boston	, Massachusetts
------------------	------------------------	--------------------	-----------------

Peter Bellermann, The National Neurofibromatosis Foundation, Inc.,

New York, New York

Jan A. Witkowski, Banbury Center, Cold Spring Harbor Laboratory,

Cold Spring Harbor, New York:

Welcome and Introduction

8:50-9:30 am Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Overview of

Project.

9:30-9:50 am William Slattery, House Ear Institute, Los Angeles, California: Overview

of NF2 Project.

9:50-10:20 am Break

10:20-10:50 am Susan Huson, The Churchill Hospital, Oxford, United Kingdom: Patterns

of Plexiform Neurofibromas in Different Anatomical Locations.

10:50-11:50 am Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Subject

Acquisition Protocols.

11:50-12:30 pm	Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Reimbursement and Administration.
12:45 pm	Luncheon at Robertson House
2:00-5:30 pm	SESSION II: MRI Protocol
2:00-2:30 pm	Diego Jaramillo, Children's Hospital, Boston, Massachusetts: MRI of Peripheral Plexiform Neurofibromas (including Protocol).
2:30-3:00 pm	Tina Young Poussaint, Children's Hospital, Boston, Massachusetts: MRI of Cranial and Spinal Plexiform Neurofibromas (including Protocol).
3:00-3:20 pm	Jay Tsuruda, University of Utah, Salt Lake City:
3:20-3:50 pm	Break
3:50-4:50 pm	Jay B. Zimmerman, WorldCare, Inc., Cambridge, Massachusetts: WorldCare MRI Protocol.
4:50-5:30 pm	James DiCanzio, Children's Hospital, Boston, Massachusetts: Statistical Analysis of Radiological Data.
6:00 pm	Reception at Robertson House
7:00 pm	Dinner at Robertson House
Monday, 8 February	
7:30-8:45 am	Breakfast at Robertson House
9:00-12:30 pm	SESSION III: Clinical and Pathological Data
9:00-10:00 am	Jan M. Friedman, University of British Columbia, Vancouver, Canada: Clinical Database.
10:00-10:20 am	Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Patient Questionnaire.
10:20-10:50 am	Break
10:50-11:30 am	David Wolfe, Mt. Sinai Medical Center, New York, New York: Histopathologic Correlates of Growth in Plexiform Neurofibroma.

11:30-12:30 pm	David Wolfe, Mt. Sinai Medical Center, New York, New York and Bruce R. Korf, Children's Hospital, Boston, Massachusetts: Pathology Review Facility.
12:45 pm	Luncheon at Robertson House
2:00-5:30 pm	SESSION IV: Tissue Bank and Cell Biology
	Studies of Cell Biology
2:00-2:30 pm	Lynn Rutkowski, Abramson Center, Philadelphia, Pennsylvania: Understanding biological defects in neurofibroma-derived Schwann cells. Part 1: Resolving obstacles.
2:30-3:00 pm	Nancy Ratner, University of Cincinnati College of Medicine, Ohio: Neurofibroma-Derived Schwann Cells are invasive and Show High Ras- GTP.
3:00-3:30 pm	David Viskochil, University of Utah, Salt Lake City: Somatic DNA Alterations in Peripheral Nerve Sheath Tumors.
3:30 pm	Break
3:30-5:30 pm	David H. Gutmann, Washington University School of Medicine, St. Louis, Missouri: Administration of Tissue Bank and Mechanisms.
6:00 pm	Reception at Robertson House
7:00 pm	Dinner at Robertson House
Tuesday, 9 February	
7:30-8:45 am	Breakfast at Robertson House
9:00-12:15 pm	SESSION V: Logistical Issues
9:00-10:30 am	Bruce R. Korf: Children's Hospital, Boston, Massachusetts:
	Time Line Publication of Policy Finance Consent
10:30 am	Break

10:30-12:15 pm

Logistical Issues (Cont'd)
Bruce R. Korf: Children's Hospital, Boston, Massachusetts

12:30 pm Luncheon at Robertson House

Afternoon departure

NATURAL HISTORY OF PLEXIFORM NEUROFIBROMAS IN NF-1

The Banbury Center, Cold Spring Harbor Laboratory, 6-9 February 1999

INVITED PARTICIPANTS

Peter Bellermann
The National Neurofibromatosis
Foundation, Inc.
95 Pine Street, 16th floor
New York NY 10005
(212) 344-6633 ext 29
(212) 747-0004 fax
bellermann@aol.com

Nancy R. Brown Open Market, Inc. 29 Thornton Road Waltham MA 02453 (781) 899-7576 (781) 359-8133 fax nbrown@openmarket.com

Rosalie E. Ferner
Department of Clinical Neurosciences
Hodgkin Building
Guy's Kings and St. Thomas' School of Medicine
St. Thomas' Street
London, SE1 9RT
United Kingdom
011-44-171-955-4162
011-44-171-378-1221 fax
r.ferner@umds.ac.uk

Jan M. Friedman
Department of Medical Genetics
B.C. Children's Hospital
University of British Columbia
4500 Oak Street, Room C234
Vancouver, B.C. V6H 3N1
Canada
(604) 875-3489
(604) 875-3490 fax
frid@unixg.ubc.ca

Robert Hopkin
Division of Human Genetics
Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati OH 45219
(513) 636-4760
(513) 636-7297 fax
hopkr0@chmcc.org

Patricia Birch
Medical Genetics
University of British Columbia
#222-6174 University Boulevard
Vancouver, BC V6T I23
Canada
(604) 822-2749
(604) 822-5348 fax
birch@interchg.ubc.ca

James DiCanzio
Dept. of Research Computing
Children's Hospital
300 Longwood Ave.
Boston, MA 02155
(617) 355-5935
(617) 278-9770 fax
dicanzio@al.tch.harvard.edu

Michael Frazier
Texas Children's Hospital
1102 Bates Street
Kleberg Genetics Center, Suite 235
Houston, TX 77030
(713) 770-4289
(713) 770-4294 fax
mfrazier@bcm.tmc.edu

David H. Gutmann
Department of Neurology
Box 8111
Washington University School of Medicine
660 South Euclid Avenue
St. Louis MO 63110
(314) 362-7149
(314) 362-9462 fax
gutmannd@neuro.wustl.edu

Susan Huson
Department of Clinical Genetics
The Churchill Hospital
Old Road, Headington
Headington, Oxford OX3 7LJ
United Kingdom
011-44-1865-226024
011-44-1865-226011 fax
shuson@immsvr.jr2.ox.ac.uk

Diego Jaramillo Children's Hospital 300 Longwood Ave. Boston, MA 02115 (617) 355-7829 jaramillo@a1.tch.harvard.edu

Fernando Kok University Sao Paulo Sao Paulo, Brazil 011-11-287-2482 fax fernando.kok@fleury.com.br

Eric Legius
Center of Human Genetics
University Hospital Leuven
Herestraat 49
3000 Leuven
Belgium
011-32-16-345903
011-32-16-346060 fax
eric.legius@med.kuleuven.ac.be

Robert Listernick
Division of General Academic Pediatrics
Box 16
Children's Memorial Hospital
2300 Children's Plaza
Chicago IL 60614
(312) 880-3832
(312) 281-4237 fax
boblist@nwu.edu

Roger J. Packer Department of Neurology Children's National Medical Center 111 Michigan Avenue Washington DC 20010 (202) 884-2120 (202) 884-5226 fax rpacker@cnmc.org Rosita Kirshman Section of Genetics Children's Hospital of Oklahoma 940 NE 13th Street Oklahoma City, OK 73104 (405) 271-8685 (405) 271-8697 fax kirshman@flash.net

Bruce R. Korf Enders 561 Children's Hospital 300 Longwood Avenue Boston MA 02115 (617) 355-6091 (617) 355-7588 fax korf@hub.tch.harvard.edu

Frank Lieberman
Department of Neurology, Box 1052
Box 1052
Mount Sinai School of Medicine
1 Gustave Levy Place
New York NY 10029
(212) 241-7581
(212) 987-3301 fax
frank_lieberman@smtplink.mssm.edu

Mia MacCollin
Neurogenetics Unit
Building 149
Massachusetts General Hospital
13th Street
Charlestown MA 02129
617-726-5725
617-726-5736 fax
maccollin@helix.mgh.harvard.edu

Scott L. Pomeroy Neurology Children's Hospital 300 Longwood Avenue Boston, MA 02115 (617) 355-6874 (617) 738-1542 fax pomeroy@hub.tch.harvard.edu Tina Young Poussaint Children's Hospital 300 Longwood Ave. Boston MA 02155 (617) 355-6450 (617) 730-0465 fax poussaint@a1.tch.harvard.edu

Lynn Rutkowski 512c Abramson Center 3400 Civic Center Boulevard Philadelphia PA 19104

Gretchen Schneider NF Clinic Fegan 10 Children's Hospital 300 Longwood Avenue Boston MA 02115 (617) 355-4699 (617) 277-5933 fax schneider_g@a1.tch.harvard.edu

Sarang D. Thakkar Department of Neurology Klinikum Nord Ochsenzoll Langenhorner Chaussee 560 22419 Hamburg Germany 011-49-40-5271-2872 011-49-40-5277-462 fax sdthakkar@aol.com

David Viskochil Division of Medical Genetics Room 413 MREB University of Utah Salt Lake City UT 84112 (801) 581-8943 (801) 585-7252 fax dave.viskochil@hsc.utah.edu Nancy Ratner
Dept. of Anatomy & Cell Biology
University of Cincinnati College of Medicine
231 Bethesda Avenue
Cincinnati OH 45267-0521
(513) 558-6079
(513) 558-4454 fax
nancy.ratner@uc.edu

Mary Sanford
Enders 561
Children's Hospital
300 Longwood Avenue
Boston MA 02115
(617) 355-3479
(617) 355-7588 fax
sanford_m@hub.tch.harvard.edu

William Slattery
House Ear Institute
2100 West Third Street
Los Angeles CA 90057-9927
(213) 483-9930
(213) 484-5900 fax
wslattery@hei.org

Jay Tsuruda Department of Radiology 50 N. Medical Drive Salt Lake City, UT 84112

David Wolfe
Neuropathology
Box 1134
Mt. Sinai Medical Center
1 Gustave Levy Place
New York NY 10029-6574
(212) 241-9145
(212) 534-1343 fax
david_wolfe@smtplink.mssm.edu

Jay B. Zimmerman WorldCare, Inc. One Cambridge Center Cambridge MA 02142 (617) 250-5180 (617) 374-9991 fax jzimmerman@mail.worldcare.com